PULMONARY FUNCTIONS IN TYPE 2 DIABETIC PATIENTS AND ITS CORRELATION WITH FACTORS AFFECTING GLYCEMIC STATUS.

Dissertation submitted in

Partial fulfillment of the regulations required for the award of

M.D. DEGREE

In

PHYSIOLOGY– BRANCH V

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CHENNAI

PSG INSTITUTE OF MEDICAL SCIENCE & RESEARCH
PEELAMEDU, COIMBATORE – 4.

CERTIFICATE

This is to certify that the dissertation titled 'Pulmonary functions in type 2 diabetic patients and its correlation with factors affecting glycemic status' is an original work done by Dr. Bhavya.R.L. Post graduate student, during the period of her post graduation in Physiology in our institution. This work is done under the guidance of Dr.R.Nagashree, Professor and HOD, Department of Physiology, PSG Institute of Medical sciences and Research, Coimbatore.

Dr.R.Nagashree
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DECLARATION

I hereby declare that this dissertation entitled “Pulmonary functions in type 2 diabetic patients and its correlation with factors affecting glycemic status’ was prepared by me under the guidance and supervision of Dr.R.Nagashree, Professor and HOD, Department of Physiology, PSGIMS&R.

This dissertation is submitted to The Tamilnadu Dr. MGR Medical University in fulfillment of the university regulations for the award of MD Degree in Physiology.

BHAVYA.R.L.

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Institutional Human Ethics Committee

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To
Dr R L Bhavya
Postgraduate
Department of Physiology
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Coimbatore

Ref: Project No. 14/400

Date: December 15, 2014

Dear Dr Bhavya,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 05.12.2014 to conduct the research study entitled *"A study of pulmonary functions in type II diabetics and its correlation with the factors affecting glycemic status"* during the IHEC meeting held on 12.12.2014.

The following documents were reviewed and approved:

1. Project Submission form
2. Study protocol
3. Informed consent forms
4. Data collection tool
5. Permission letter from concerned Heads of department
6. Current CVs of Principal investigator, Co-investigators
7. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 12.12.2014 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Dr. P. Sathyan (Chairperson, IHEC)	DO, DNB	Clinician (Opthalmology)	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr. S.Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Dr. D. Vijaya	M Sc, Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

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Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
   d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
   e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
   f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

15.12.14

Dr S Bhuvaneshwari
Member-Secretary
Institutional Human Ethics Committee

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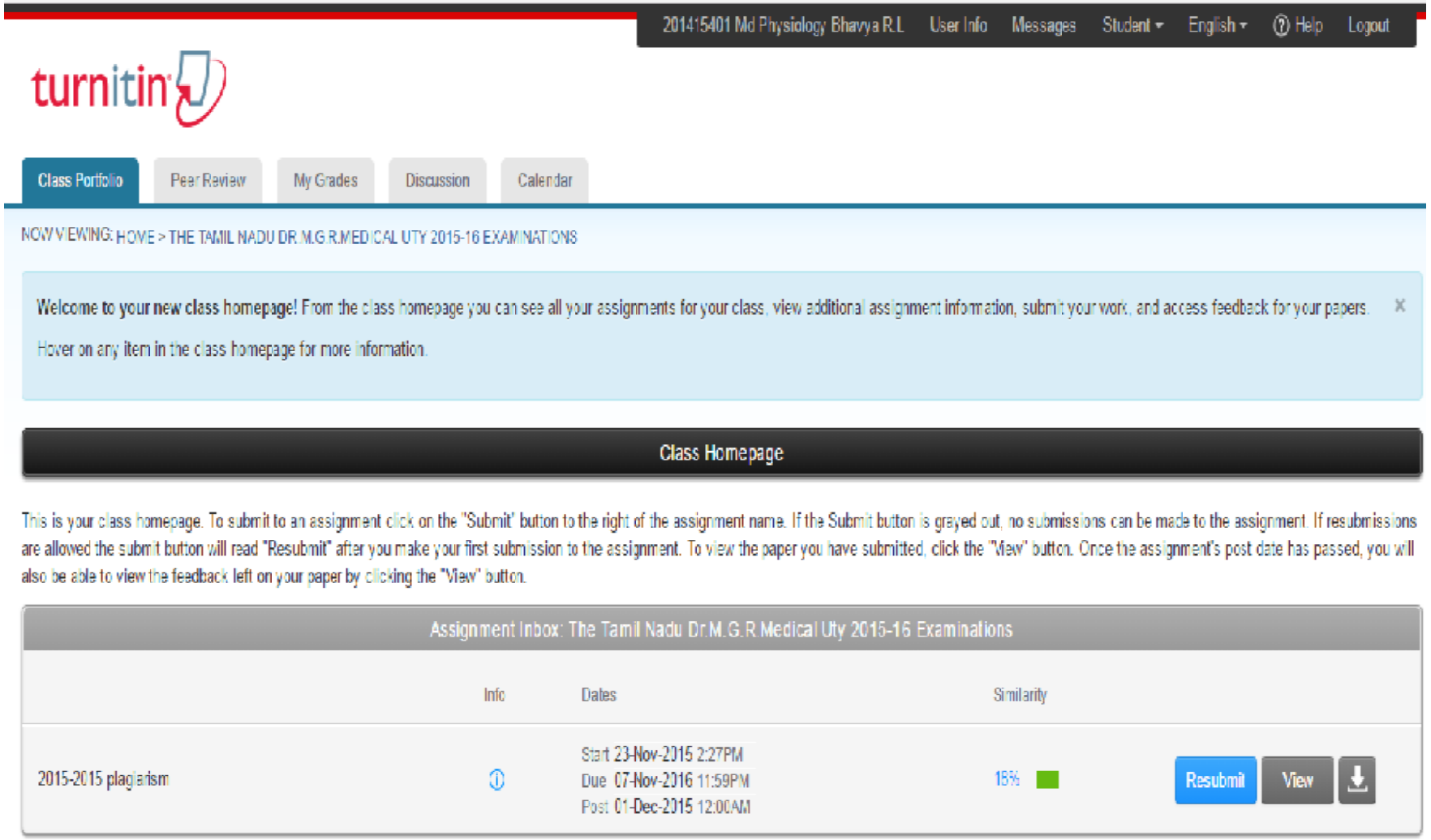
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Lastly, I pray and thank the Almighty and express my thanks to all the volunteers involved in the study without whom this study would have been not possible.

CONTENTS

INTRODUCTION

DIABETES MELLITUS:

Diabetes mellitus (DM) is a major public health problem worldwide. According to WHO, India will be a world diabetic capital in 2025. [1]

Diabetes mellitus (DM) is a metabolic syndrome, which affects multiple organ systems in the body. There is a drastic increase in the incidence and prevalence of DM in Asian Indians. [1]

In India the total number of people suffering from diabetes would be around 87 million in 2030 according to an estimate by International Diabetes Federation(IDF).[2]

In diabetes mellitus (DM) is there occurs disturbance of carbohydrate, protein and fat metabolism. DM is due to defect in insulin secretion, insulin action or both which is characterized by chronic hyperglycemia. [3]

The major risk factors for developing diabetes are increasing age, physically inactive lifestyle and obesity.

Obesity predisposes to insulin resistance. Circulating levels of insulin may be normal or increased in such people yet inadequate to control blood glucose levels due to insulin resistance. Their glycemic status can be brought to control by weight reduction and anti-glycemic drugs as insulin resistance can be improved with weight reduction. [3]

A diabetic patient may have symptoms like visual blurring, polydipsia, polyuria, polyphagia. The patient may also present with marked weight loss. In severe uncontrolled diabetes the patient can go in for diabetic ketoacidosis. Negligence, improper drug intake by the patient or lack of effective treatment will ultimately end up in diabetic coma and death.

CLASSIFICATION OF DIABETES MELLITUS:

Diabetes can be broadly classified into type I and type II.

Type I diabetes is due to destruction of β-cell which leads to deficiency of insulin. Type II results from insulin resistance with relative insulin deficiency.[4, 5]

Type II diabetes is more common. A person diagnosed with type II diabetes will have disorders of insulin action and insulin secretion. There occurs progressive destruction of β-cells as disease duration increases [6]

Type-II DM does not produce classic symptoms as hyperglycemia. It develops only gradually and hence difficult to diagnose in the early stage itself. Diabetes is often diagnosed as a result of routine blood or urine investigations. Therefore, by the time a person is diagnosed to be diabetic, would have developed many functional as well as pathologic changes in the body.

Long term effects of diabetes include failure and dysfunction of various organs which includes blood vessels, kidneys, heart and eyes. Patients are at high risk for developing microvascular and macrovascular complications.

Micro-macro vascular pathologies can have detrimental effects on many organs. The various micro vascular complications such as retinopathy, nephropathy and neuropathy are well documented. However, the lung disorders that occur due to diabetes have poor documentations with variable results. [7]

The involvement of lung remains asymptomatic until late stages of the disease. The scleroproteins collagen and elastin, which forms the major tissue proteins in bronchi, pulmonary vessels and interstium, are altered due to hyperglycemia there by affecting the pulmonary functions.

In normoglycemic individuals there occurs enzymatic glycosylation of proteins, which is essential for the proteins to become functionally active. Enzymatic glycosyltion is actually a part of post-translational modification of proteins, which is catalysed by enzymes. In some cases, this process is essential for the proteins to function as enzymes.

Thus in this process there occurs addition of sugar or saccharide derivative to the protein, in the presence of an enzyme. Whereas, in hyperglycemic individuals there occurs non-enzymatic glycosylation of proteins.

Non-enzymatic glycosylation in other terms is called as glycation. Here there is addition of sugar to protein in the absence of enzymes. Once the protein becomes glycated, its function markedly reduces. Thus enzyme activity of these proteins are reduced. The end-products of glycation are called as advanced glycation end products (AGEs). These products on long term basis gets deposited in the tissues especially collagen, elastin and lens crystallins. Once deposited, then

this process becomes irreversible. These proteins then cannot fold upon themselves and they lose their normal functions. And their normal turnover is dropped and they can't be properly recycled. This can lead to too many pathologic processes, which ultimately ends up in diseases. [8]

Non- enzymatic glycosylation (glycation) of elastin and collagen leads to thickening of basement membrane and microangiopathy which in turn may restrict lung volumes and capacities leading to development of restrictive pattern of lung disease. [1] This can potentially incapacitate the patients and further worsen their quality of life. Hence assessing the pulmonary status of these patients at the outset is essential in retarding the progression of the disease, its management and prognostication.

These alterations can be delayed by maintaining blood sugar within normal range. These changes can also be seen as age advances but progression and intensity of changes are more pronounced in patients with diabetes mellitus. [9]

Pulmonary Function Tests (PFT) are widely used to provide a measure of lung function for assessing and quantifying pulmonary impairment in various clinical conditions and for monitoring response to therapy, effect of environmental, occupational and drug exposures-associated with lung diseases.

SPIROMETRY:

Spirometry is the most common and most useful lung function test that has extensive clinical implications. It is an easy test to perform and is widely available at hospitals. Measurement of respiratory volumes and capacities is an essential tool for determining how well the lung is functioning.

Assessment of mechanics of lung and chest wall, lung volume and capacities will help to screen for any obstructive or restrictive lung pathologies.PFT also will help to document the progression of lung disease and effectiveness of any therapeutic intervention.

Spirometry has static as well as dynamic components.

Static – Includes lung volumes

Dynamic – Includes time

Subjects can be categorized to have normal pulmonary function or obstructive and restrictive lung pathologies based on the dynamic PFTs.

Patients with an obstructive pattern as in conditions like asthma, bronchitis will have decreased air flow where the rate at which air can be expelled from the lungs is affected and this condition is characterized by decrease in FEV_1 (forced expiratory volume at the end of first second) , normal FVC (forced vital capacity) and low FEV_1 to FVC ratio. An FEV_1/FVC ratio of $\leq$ 0.7 (70%) confirms obstructive pathology [10].

In restrictive pattern of lung disease which occurs in conditions like kyphosis, scoliosis, lung fibrosis will affect the lung expansion which can result in reduced lung volumes or total lung capacity with a normal air flow. That is here FEV_1 and FVC values are reduced with a normal FEV_1 /FVC ratio. [11]

The load- bearing elements also the structural proteins of the lung parenchyma that is the connective tissue components (collagen and elastin) undergo non-enzymatic cross- linking during aging and in diabetes.[12]

In diabetic individuals non enzymatic glycation of these proteins will result in the formation of advanced glycated end-products that can lead to structural and functional changes in the collagen-elastin fibre network. This can affect the alveolar duct wall which in turn will affect the micromechanics of lung parenchyma i.e. the elastic recoiling of the lung will be affected that in turn will affect the rate at which the air is forced out**.**

The effect of diabetes on lung functions was proved by a study conducted by Plopper et al. [13] The study was done in rats. In this study, diabetes was induced in rats with the help of streptozotocin. Then on studying the histology of pulmonary tissue it was found that, there were changes in the structure of granular pneumocytes, scleroproteins present on the wall of the alveoli[14] and clara cells.[15] It was postulated that these changes could be due to the side effects of the drug itself. However, a study done by Kida et al. [14] showed that these were due to

the deficiency of insulin.The adverse effect of diabetes on lung functions were demonstrated in the post-mortem studies done on the diabetic patients. It showed thickening of basement membrane of capillaries of alveoli, which suggested microangiopathy. [16] Microangiopathy was also reflected on the alveolar septal capillaries as well as on the alveolar and pleural arterioles. [17, 18]

AIMS AND OBJECTIVES

AIM:

To assess the pulmonary functions of diabetic patients.

OBJECTIVES:

1. To assess and compare the pulmonary functions of diabetic patients with age and BMI matched healthy individuals.

2. To correlate the lung functions of diabetic patients with their BMI (Body mass index) and HbA_1c (glycosylated hemoglobin).

JUSTIFICATION:

- ✓ The pulmonary complications of Diabetes mellitus can have severe impact on the quality of life of the affected individuals.
- ✓ The studies related to the effect of diabetes on pulmonary functions are relatively few and there is lack of adequate data on Indian population.
- ✓ This study will focus on the pulmonary dysfunction, maximal forced spirometric pulmonary function tests to be specific.

REVIEW OF LITERATURE

There is an alarming increase in the incidence and prevalence of DM in Asian Indians. [1] In India the total number of people suffering from diabetes would be around 87 million in 2030 according to an estimate by International Diabetes Federation(IDF).[2]

A report by WHO predicts that the prevalence of diabetes among adults around the world would increase up to 300 million in 2025. [1]

Developing countries had an approximate of 84 million diabetics in the year 1995[19] .WHO suggests that in 2025 the percentage of diabetics would rise up to 57.2 million in India [1] So approximately 75% of the population is prone for diabetes in future. Urban areas have been reported to have high prevalence for DM [20] .It has increased from 2.1% in early 1970, to 11.6% in 1996[21].

Though the rate of conversion of impaired glucose tolerance to full prone DM is low, many people are subjected to the risk of developing the same. [22]

Diabetes mellitus, a metabolic syndrome characterized by hyperglycemia occurs due to derangement in the metabolism of carbohydrate, protein and fat. [23]

Classification of diabetes is now based on:

1. Clinical stages
2. Etiological types

In 1997 the American Diabetes Association (ADA) proposed clinical classification of diabetes[4] Later in 1999 the World Health Organization (WHO) adopted this classification.[5]

Clinical stages of diabetes:

1. Stage of normal glucose tolerance

2. Stage of impaired glucose regulation (Impaired glucose tolerance/ Impaired fasting glucose).

3. Stage of diabetes mellitus

- Not insulin requiring
- Insulin requiring for control
- Insulin requiring for survival

Etiological classification:

1) Type1:

Due to destruction of β-cell. This condition leads to absolute insulin deficiency.

Causative factors:

- Autoimmune conditions
- Idiopathic

2) Type 2:

Due to insulin resistance.

This condition is characterized by relative deficiency of insulin.

Causative factor:

Defect in secretion of insulin. This defect in secretion can be either with insulin resistance or without insulin resistance.

3) Gestational diabetes

4) Other types of diabetes:

- β cell dysfunction due to genetic causes.
- Defective action of insulin due to genetic defects.
- Infections
- Diseases of exocrine pancrease.
- Endocrinopathies.
- Immune mediated diabetes
- Drug or chemical induced diabetes
- Diabetes associated with genetic syndromes.

Criteria for diagnosis of diabetes [24]

1. Fasting plasma glucose - ≥ 126 mg/dl or ≥ 7.0 mmol/L
2. Two-hour plasma glucose - ≥ 200 mg/dl or ≥ 11.1 mmol/L
3. HbA1c - ≥ 6.5 %

Risk factors for diabetes [25]

- Hereditary factors
- Ethnicity
- Positive history of previous gestational diabetes
- Unhealthy dietary practices
- Sedentary life style
- Over weight, Obesity
- Smoking

The commonest risk factor for type 2 diabetes is excess weight gain owing to unhealthy dietary habits and physical inactivity.

Physical inactivity together with overweight and obesity poses the greatest risk for the cause of global diabetes burden[26] But this association varies in different set of population.[27] Diabetes develops in South-East Asians at a lower range of BMI as when compared to Europeans.[28]

Common diets that pose the risk of type 2 diabetes are:

- High consumption of saturated fats
- Excess intake of total fat
- Less consumption of dietary fiber[29,30,31]
- Beverages containing free sugars[32]

The new WHO report is emphasizing the government to make sure that every individual is able to take up healthy choices and that the system of health care should be able to make the diagnosis, provide treatment and care for those with diabetes. It encourages every individual to eat healthy, be active, physically fit and prevent excessive weight gain. This was issued by WHO on world health day 2016, which made a call for effective action on diabetes in both prevention as well as treatment [33]

OBESITY:

Obesity is defined as weight about ≥ 20% of average weight per height [34].A body mass index of more than 30mg/kg2 is considered as obese.

The different classes of BMI values which are used to categorize a person as obese or normal is calculated by the formula:

Weight in kg / (Height in meter) [34]

BMI in kg/m^2	CATEGORY
1. < 18.5	Underweight
2. 18.5 – 24.9	Normal
3. ≥ 25.0 – 29.9	Overweight
4. ≥ 30	Obese
5. 30 – 39.9	Obese class 1
6. 40 – 49.9	Obese class 2
7. ≥ 50	Obese class 3

OBESITY AND DIABETES:

Obesity is known to cause a low grade inflammation. The chronic inflammatory process is characterized by rise in blood levels of pro-inflammatory cytokines gain an access through blood stream to cause systemic inflammation .[35] This can cause insulin resistance.

A recent study showed that treatment with salicylate can cause improvement in insulin resistance. [35] Studies show that lifestyle changes and certain therapies that reduce obesity can prevent diabetes. [36]

OBESITY AND LUNG FUNCTION:

Obesity can cause marked reduction in lung volumes and capacities. The mechanism behind reduction in lung functions is attributed to the fact that in obese individuals there is mechanical limitation to the abdominal and thoracic movements owing to increased fat deposition in these areas. This can cause reduction in the compliance of chest wall and air flow limitation leading to reduced lung function.[37]

In obese individuals the increased abdominal obesity restricts the downward movement of the diaphragm. This limits the lung expansion thereby decreasing the total lung capacity. This is proved by the fact that weight reduction helps in increasing the total capacity. [38, 39]

Fat deposition in sub-pleural spaces can possibly reduce the volume of chest cavity which in turn can affect the lung volumes.[40]Metabolic rate in obese individuals are high. Hence, there is an increase in consumption of oxygen and production of carbon dioxide. Thus, minute ventilation is increased in such individuals. As the compliance of the thoracic wall is decreased in these individuals, the work of breathing is increased and the respiratory reserve volume and vital capacity is reduced. [41]

Thus due to alteration in the ventilation-perfusion ratio the person may develop hypoxia and hypercapnia leading to respiratory acidosis.

As discussed earlier increase in prevalence of diabetes is attributed to following factors:[42]

- Genetic predisposition
- Unbalanced diet rich in carbohydrates and fats
- Sedentary life style
- Stress

One of the common reason for stress and sedentary life style are fast urbanization. A report by WHO states that the annual cost for diabetic care in 2002 was Rs.12, 000 for those on insulin and Rs 2400 for those on oral hypoglycemic. So almost 75.2 billion is needed for a standard treatment for an estimate of 20% treated with insulin among the 17.3 million affected with diabetes in India. [12]

A study conducted in The United States of America shows that about 6% of women and 11% of men who are diabetic and between 45 to 65 years are reported to have myocardial infarction. Compared to the non-diabetics the risk percentage for MI in diabetic men and women are 4 and 2.5 times higher respectively.

There is high risk of atherosclerosis even in pre-diabetic individuals. Among the type -2 diabetics around half of middle aged men and women are found to have symptomatic CHD, the moment their disease is diagnosed [(43).] The development of atherosclerosis is gradual which results in hyperinsulinemia and hyperglycemia even before actual onset of type- II DM [(44).]

Hyperglycemia is the main cause of non-enzymatic glycosylation of the scleroproteins. The study defines glycation as the formation of complexes between amino acids and sugars, which is the reason for browning and hardening of food on heating.

MAILLARD REACTION / ADVANCED GLYCATION:

The chemical reactions that results in non-enzymatic glycation of proteins by reducing sugars is known as Maillard reaction.

Glycotoxins or advanced glycation end products(RAGEs) are formed as a result of cross reaction between amino acids and reducing sugars[45] which is the reason for different pathologies in diabetes. The presence of these moieties in vivo is unknown but tissues of diabetics show elevated levels of these moieties [46].

Protein glycation can be reduced on administration of vitamin E.[47]The toxic moieties formed due to glycation contribute to the developing renal, neurological, vascular, and atherosclerotic changes in old age and diabetes. The accumulation of toxic products at the sites of neuronal degeneration has been observed in Alzheimer's disease[48].

Non-enzymatic glycation of proteins can lead to multi system disorders like: End stage renal disease, blindness, stroke, ischemic heart disease, neuropathy, peripheral vascular disease.[49] All these complications can be reduced by preventing the cross link formation between proteins and reducing sugars and also by preventing the accumulation toxic moieties that is advanced glycation products in the body. This can also be achieved by inhibiting the glycation products by blocking their receptors by means of certain drugs and this requires adequate knowledge about the various mechanisms underlying the pathogenesis of diabetes. Pyridoxamine and aminoguanidine are proved to prevent the formation of AGE's in animal models[12].

MECHANISM OF FORMATION OF ADVANCED GLYCATION PRODUCTS:

A study by R B Nawale et al. suggests that high sugar levels is an important factor which can lead to glycation of lysine residue of protein which can affect their function. The process of advanced glycation is initiated when glucose reacts with amino acid residues of proteins to form certain moieties[50]which results in the formation of Schiff bases that inturn are converted into Amadori products[51] .

Amodari products undergo rearrangement and cross linkage to form advanced glycated end products (AGEs) that can alter the structure and function of proteins which is common in diabetes and aging. [52] These reactions take place at a slow rate so only proteins with long half-lives and those containing lysine residues eg. collagen undergo glycation.

when sugar levels are high the rate at which glycation takes place is markedly elevated and the renal clearance of these adverse moieties are decreased and the receptors for AGEs are increased , which can lead to age mediated cell activation and amyloidosis[53].

DISTRIBUTION AND ROLE OF ELASTIN FIBERS IN LUNGS:

The micromechanics of lungs are mainly attributed to the connective tissue network in the lung parenchyma. Connective tissue fibers are found on the alveolar duct wall in high concentration.

A ring like structure which is continuous is formed around the mouth of each alveoli. The elastin fibres tend to pass deep into the septal wall of the alveoli.

Elastin fibers are broadly distributed in tissues like lung parenchyma, pleura, certain ligaments and arteries. The elasticity of these fibers allows them to stretch and can cause elastic recoiling as and when required.[54]

DISTRIBUTION AND ROLE OF COLLAGEN IN LUNGS:

The structural integrity of the lung tissue is mainly dependent on the collagen fibers. Collagen especially type1 and type 2 is distributed widely in the interstitium of the lung. Collagen fibers also act as a connecting bridge between the visceral pleura and the alveolar ducts. Thus collagen plays an important role as a load bearing element of alveolar duct and wall.[55] Collagen and elastin fibres are found to be closely associated and connected to each other.[56]Thus collagen is found to play an equal and important role in lung elasticity.[57]

Collagen helps in preventing over stretching of the lung matrix. The cross linking between the collagen fibers, number of fibrils and its diameter determines the stiffness of the collagen fibers that is enhanced cross linking and increased diameter of the collagen fibers have the tendency to increase the stiffness of normal collagen. [58, 59]Type 1 collagen is found to be stiffer than type 3 and both of them play an important role in fiber stiffness.

ROLE OF INTERSTITIAL CELLS IN LUNG MECHANICS:

The smooth muscle cells located in the alveolar ducts, walls of blood vessels as well as the myofibroblasts of the alveolar walls play important role as contractile cells.[60]The viscoelastic properties of lung can be moderately modified by the stress generated by the stimulation of these fibers.[61] But the main role of these cells are in the active repair of the connective tissue.[62]

Surface tension forces acting on the lung tissues play an important role in micromechanics of lungs.[54]Surfactant produced by the type 2 pneumocytes lines the alveoli and airways which contributes to stability of alveoli and prevents it from collapse when the lung volume goes down.[63]Studies show that the quantity of surfactant produced and its composition depends on the pattern of stretching of the lung parenchyma.[64]

LUNG AS A TARGET ORGAN IN DIABETES:

The discussion shows that apart from other complications of diabetes such as retinopathy, nephropathy and neuropathy, lung also is a target organ in a person with long standing diabetes. The non-enzymatic glycosylation of the scleroproteins which are widely distributed in the chest wall and bronchial tree and enhanced cross link formation between the collagen fibers are attributed to the marked reduction in the mechanical function of lungs.[65]More over any change in the quality and quantity of collagen can lead to restrictive impairment in lung function.[66]As collagen is non enzymatically glycosylated in diabetic individuals they exhibit resistance to digestion by collagenase and pepsin as compared to

normal non-diabetic healthy individuals.[67]Adding on to it, the reduction in the normal turnover of collagen fibers can lead to reduction in the compliance of the lung parenchyma. As compliance of lung decreases restrictive type of ventilatory defect develops in the diabetic lung.[68] The mechanical function of lungs which is determined by its elasticity can be tested by spirometric pulmonary function tests.[69]

Restrictive pattern of lung function can be determined by low values of spirometric pulmonary function tests. [10]

Lung volumes:

1. Forced vital capacity (FVC) – It is the maximum volume of air that can be exhaled forcefully and rapidly with effort after a deep inhalation. The test becomes significant only if the person can exhale forcefully for six seconds or more.

Normal value is 80-120%

In diabetic individuals this value is reduced. This is attributed to increase in formation of cross linkage between polypeptides of collagen embedded in the connective tissue matrix of lung parenchyma.

2. Forced expiratory volume at first second (FEV_1) – It is the volume of air that is exhaled in the first second of maximal exhalation after a deep inspiration.
This is a useful tool to assess, how rapidly the lungs can be emptied.

Normal value is 80-120%.

In diabetic individuals this value is also decreased. This is also attributed to the stiffening of the lung parenchyma due cross link formation between collagen fibers as a result of enhanced glycosylation of collagen fibers due to hyperglycemia.

3. FEV_1 / FVC:

The best index of airflow limitation can be given by the ratio of FEV_1 to FVC.

Normal value that is the absolute ratio should be within 5% of the predicted ratio. Here FEV_1 is expressed in terms of percentage of FVC.

In diabetic individuals with restrictive pattern of lung disease, this value is either normal or increased that is $\geq$ 70%.

4. Peak expiratory flow rate (PEFR) – This flow rate is reached immediately by the first bout of air as the person exhales. This helps to assess the following parameters:

- Helps to judge if the person is putting in maximum effort during the procedure.
- Quality of the test
- Strength of muscles of expiration
- Condition of large airways

In diabetic individuals due to modification of collagen and elastin ratio the mechanical properties of lungs are altered which reflects as reduced compliance

and poor elastic recoil of lungs. All these factors will affect the peak expiratory flow rate.

5. $FEF_{25-75\%}$:

This shows the forced expiratory flow in the middle half of forced vital capacity that is the average flow from the point at which 25% of forced vital capacity has been breathed out to the point at which 75% of forced vital capacity has been breathed out. This indicates the patency of small airways.

In a person who is diabetic for a long period the lung may be subjected to damage. This chronic status of lung disease will first be represented in the smallest airways and in the flow volume loop this early damage will reflect towards the end of the expiratory part of the loop. This may be due to poor elastic recoil forces and poor muscular support of the respiratory system which is essential for forced expiration.[70]

Certain studies have shown that activity of the enzyme lysyl oxidase is increased in rats which developed diabetes that was experimentally induced. This enzyme is involved in connective tissue formation. Thus in diabetic individuals enhanced activity of these enzymes will lead to thickening of alveolar interstitium.[71]

INVOLVEMENT OF RESPIRATORY MUSCLES AND NEUROMUUCULAR FACTORS IN DIABETES:

Loss of force generating capacity of the muscles of expiration can result in reduction of peak expiratory flow rate along with poor elastic recoiling of lungs.[72,73] Similarly FEF25-75% is said to depend on both the neuromuscular factors as well as the mechanical properties of the respiratory system as FEF25-75% depicts nothing but the initial part of forced vital capacity.[74]

These factors show that the muscles of respiration are involved in diabetes. This can be due to enhanced protein catabolism owing to high blood glucose level. This can ultimately lead to poor strength of skeletal muscles. [75]

The defect in respiratory pump mechanism is also attributed to development of diabetic polyneuropathy. As glycosylation causes thickening of the basement membrane in almost all tissues, they can cause demyelination as well as chromatolysis of axon as well as Schwann cells apart from microangiopathy.[76]Thus it shows that thoracic nerves and phrenic nerve, which are predominant nerve supply for the muscles of respiration including diaphragm is affected in diabetic individuals.[76,77]

ROLE OF OXIDATIVE STRESS IN LUNG DYSFUNCTION:

High blood sugar level can lead to endothelial dysfunction. Increased blood sugar level can increase the endothelial cell production of free radicals. This can impede with the vessel dilatation.[78]This occurs due to oxidative stress. It is

proved as this process can be reversed by treatment with antioxidants or L-arginine.

The mechanism behind this is that, the free radical production due to high blood sugar results in the activation of protein kinase-C and nuclear factors. This results in formation of AGEs within the cells. [79] Hyperglycemia can lead to increase in production of superoxide anion. This leads to increase in the levels of superoxide than nitric oxide within the endothelial cells, which ultimately results in the production of nitrotyrosine and peroxinitrate. The major marker for oxidative stress is nitrotyrosine. In patients with endothelial dysfunction and in those with diabetes the nitrotyrosine level seems to be increased. [80,81]Thus it shows that oxidative stress can lead to endothelial dysfunction in diabetic subjects.

This process can affect the respiratory apparatus in diabetic patients. The oxidative stress induced by hyperglycemia can lead to loss of integrity of pulmonary capillary endothelium, which in turn can affect the gas exchange process across the respiratory membrane. This can also affect the blood volume in the lung capillaries, as acute increase in blood sugar can suppress vasodilatation due to oxidative stress.[69]

Similarly markers of inflammation in the epithelial lining fluid of lungs can be assessed by measuring the markers of inflammation in the exhaled breath condensate. It was found that the concentration of leukotrine B4 was increased four times in patients with chronic obstructive pulmonary disease with diabetes

than those without diabetes.[82] Studies suggests that oxidative stress induced by high blood sugar level is attributed to non-enzymatic glycosylation of proteins along with low plasma levels of ascorbate. The ideal measure for oxidative stress is urinary F2 isoprostanes. This was found to be increased in diabetic subjects. But studies have shown that supplementing these people with α-tocopherol tends to decrease the levels of isoprastanes in urine.[78]Another study shows that 1250 mg of vitamin c, 680 units of α-tocopheral given for four weeks daily resulted in reduction in albuminuria.[83]Another study showed that treating type1 diabetic subjects with 1800 units of α-tocopheral for four months daily showed improvement in blood flow to retina and creatinin clearance.[84]

GLYCOSYLATED HEMOGLOBIN AND ITS ASSOCIATION WITH PULMONARY FUNCTION TESTS:

The rate of formation of glycation products is proportional to the concentration of blood sugar.[85]So glycemic control must have some correlation with the pulmonary function tests in diabetic individuals. Glycemic control in a diabetic individual can be assessed by measuring the level of glycosylated hemoglobin (HbA1c). HbA1c value serves as an indicator of control of blood sugar over a short term period of one to three months.

A person with HbA1c <7% is said to be under control and those with HbA1c more than 7% is said to have poor control of blood sugar.[86]If HbA1c is more than 7% then the rate of glycation of tissue proteins will be on higher side.

Thus glycation of collagen and elastin can affect the lungs and will cause decrease in the values of pulmonary function tests.

Increase in glycosylated hemoglobin can interfere with diffusion capacity of the lungs due to poor affinity of glycosylated hemoglobin to carbonmonoxide.

REVIEW:

A study conducted by Sanjeev Verma et al.[87] suggests that non-enzymatic glycosylation of collagen and elastin in lungs due to hyperglycemia can affect the mechanical function of lungs which can manifest as altered lung volumes. The reason behind it may be microangiopathy. As pulmonary interstitium, vessels, major bronchi are rich in collagen, lung functions are affected in diabetes. Though these changes are common in old age the severity of this condition is more pronounced in diabetes. The alteration in scleroproteins is reversible to begin with, so if blood glucose levels are maintained within normal range the progression of this condition can be delayed.

In this study pulmonary functions were compared between type I, typeII diabetics and normal controls. PFT was done using computerized Medspiror. Apart from this a comparison was done between anthropometric variables like height, weight as well as body surface area in diabetic individuals that includes both males and females. The study found no significant difference between male and female subjects.

A study by Sreeja et al.[88] found no significant difference in anthropometric variables between male with diabetes and normal control. This study was done to interpret the pulmonary function in diabetics on oral hypoglycemic and those on insulin with normal subjects.PFT was done with Pesomedicare smart Spirometer .The study found reduction in FEV1 and FVC% in diabetics on both oral hypoglycemics as well as insulin therapy as compared with the normal subjects.

The study shows that there is reduction in FEF 25-75%(forced expiratory flow rate) in diabetics who were on oral hypoglycemics as compared to controls.

A study by Lange et al. was done to interpret the effect of plasma glucose and diabetes on lung functions especially FVC and FEV1.Pulmonary function test was carried out with Monaghan N 403 spirometer. The study showed reduction in FVC and FEV1 values in both type I and type II diabetics but the value was reduced more in diabetics on insulin compared to those not on insulin .[89]

A study by Schnapf et al. showed reduction in lung volumes as well as in mobility of joints in type II diabetics[90]This proves that non enzymatic glycosylation of connective tissue(collagen) occurs in people with high plasma glucose[91].

One of the confounding factors that can affect the values of FEV1 and FVC is obesity. Most of the type II diabetics are obese [92]. But the study done by Lange P et al. shows that pulmonary functions were reduced in type I diabetics as compared to type II and BMI in type I diabetics is lower than that of the controls.

The study concludes that there is significant reduction in lung function in diabetics treated on insulin than those on oral treatment and diet.

A study by Davis et al. [93] has suggested that chronic complications of type II diabetes will include limitation of air flow and also reduction in lung volumes. The study proved that vital capacity,FVC,FVE1and peak expiratory flow rates are reduced in type II diabetics.

A study by Anasuma et al. [94]. shows considerable reduction in the forced vital capacity in Japanese diabetic patients in comparison to controls

A study by Ramirez et al. showed considerable difference in FVC in diabetics on oral hypoglycemics and those on insulin treatment[95].

A study by Femognari et al. showed that diabetics suffer from restrictive pattern of lung function due to reduction in FVC and FEV1 and normal FEV1/FVC.[96]

Another study by Nakajima et al. [97]. showed restrictive pattern and not obstructive pattern of pulmonary function that may be associated with metabolic syndrome. In this study metabolic factors and percentage of predicted forced vital capacity (%PFVC) were compared. %PFVC is an indicator of lung compliance. It was found to have correlation with metabolic abnormalities Abnormal lung functions were caliberated based on the lower limit of normal (LLN) which was according to American Thoracic society /European Respiratory Society guidelines[98].

Restrictive pattern of lung disease in metabolic syndrome was correlated and assosciated with C- reactive protein which is strong indicator of metabolic syndrome. In this study confounding factors such as obesity was taken into account since central obesity has impact on lung function. It results in restrictive pattern of lung function as expansion of diaphragm is affected due to central obesity. Hence waist circumference was also taken into consideration. Cut-off for waist circumference was taken as ≥90 cm for men and ≥80 cm for women. Apart from this other factors which correlate with metabolic syndrome such as lipid profile especially triglyceride level >1.70mmol/L , high density lipoprotein<1.05mmol/L , fasting blood glucose ≥ 6.11 mmol/L , blood pressure ≥ 130/85mmHg were also taken into consideration.

PFT was done using Autospiro-507 in standing position. % PEFR obtained by dividing observed FVC to that of predicted FVC. Air way resistance was measured by taking FEV1/FVC ratio. The study shows association between restrictive patterns of lung function and metabolic syndrome. [97]

A study done by Muhammad et al. [99] showed that diabetic subjects also had associated increase in triglyceride levels as when compared to normal subjects.PFT was done using Med Graphics profiler. In this study apart from FVC,FEV1, its ratio and PEFR, slow vital capacity (SVC) was also taken into account. The study showed statistically significant relation between diabetes and hypertension with a P value <0.001 and also showed high triglyceride levels in diabetics, which also had a P value of <0.001.The study shows a reduction in FVC,FEV1, in diabetic subjects but no much difference in FEV1/FVC ratio and

maximum mid expiratory flow (MMEF).The major limitation of the study was a small sample size, then the association between blood sugar control and lung function was not correlated, then the diffusing lung capacity was not assessed due economic issues.

A study conducted by Meo et al. [100,101] has showed a relation between disease duration and lung function. The lung function was found to be reduced with a dose effect relation of duration of diabetes. They found marked reduction in FVC,FEV1 and PEF in diabetic subjects as when compared to normal subjects.

An Indian study showed impairment of diffusion capacity for carbon-monoxide in diabetics especially Asian Indians. In this study subjects were divided into three groups.

Group 1: Type 2 diabetics with microvascular complications

Group 2: Type 2 diabetics without any microvascular complication.

Group 3: Normal healthy individuals.

Patients with microangiopathies were selected based on the expert opinion.

Criteria for diabetic retinopathy:

Patients with non proliferative macular edema.

Criteria for diabetic nepropathy:

1. 24 hour urine test was done to detect loss of >300mg of albumin in urine.

2. Criatinine clearance was calculated.

Criteria for diabetic neuropathy:

1. Loss of >2 stretch reflexes in legs.

2. Decreased tactile sensations, kinesthesia, Pallesthesia

Criteria for microangiopathy:

1. History of myocardial infarction or cerebrovascular accidents.

2. Changes in ECG, ECHO along with clinical examination concluded cardiovascular problems.

Criteria for Peripheral neuropathy:

1. Loss of at least two peripheral pulses.

2. Chronic ulcers of foot .

The study concludes that diffusing capacity of carbon monoxide was found to be markedly reduced in group one individuals and the parameters like FVC,FEV_1, PEFR,MIP,MEP were comparable with other groups[(102)] .The results of spirometry was interpreted based on the guidelines given by the American thoracic society. The major limitation of this study was a small sample size.

Swathi et al. [103] showed that restrictive pattern of lung dysfunction is attributed to connective tissue glycosylation, decrease in elastic recoil of lungs and inflammatory changes. But the study has shown no association between lung pathology and glycemic status or duration of disease. The study says that pulmonary complication in diabetes has been poorly documented with conflicting results. There occurs microangiopathy of pulmonary capillary network. However, due to its large reserve, the loss of microvascular bed can be overcome without developing any difficulty in breathing. Thus, the condition remains sub-clinical.

- Many studies have suggested the following pulmonary changes in a diabetic:
- Decreased lung volume
- Poor elastic recoil
- Poor performance of respiratory muscle[104,105]
- Chronic low grade inflammation
- Reduction in diffusion capacity for carbonmonoxide[106]
- Autonomic neuropathy of respiratory muscle[107]

Thus in a diabetics the lung function will deteriorate leading to loss of pulmonary reserve. The study shows significant reduction in FVC and FEV_1 but no change in their ratio[103] Similar reports have been shown in other studies[108-111].PFT was done using Helios 702 spirometer.The study found that except for ratio of FEV1 to FVC all others were reduced and the study says that the association between FVC , FEV1, duration of diabetes and glycosylated

hemoglobin is statistically insignificant as P value was >0.05[102].There is marked reduction in the vital capacity in diabetics and they were found to have restrictive of lung function [112,113]

Uchida et al. showed decreased diffusion capacity of lungs in diabetics with a defect in perfusion on ventilation scintigrams[114].

A study conducted in western Australia by Davis, et al.[111] showed that VC, FVC, FEV1, and PEFR were decreased in diabetic subjects that is between 1.1% and of 3.1% predicted values .Ehrlich et al. [115] showed that type 2 diabetics are prone to develop asthma, fibrosis ,COPD,pneumonia

A study by Benbassat[116] showed no reduction in lung functions in diabetics except that the ratio of residual volume to total lung capacity was increased in non insulin dependent diabetes patients when compared to insulin dependent diabetics. The study states that Dlco was not affected in those with microangiopathic changes when it was corrected for alveolar volume.

A study by Fawn Yeh et al.[117,118] says that in Asian Indians with metabolic syndrome or diabetes mellitus there is marked reduction in pulmonary functions. The study suggests that these people develop reduced lung function even prior to development of metabolic syndromes due to the adverse effects of obesity. The reason behind it is attributed to inflammation which results due to obesity of this arti. Diabetes care). The study showed that the percentage predicted values of forced vital capacity and forced expiratory volume at 1st second both were lower in participants with metabolic disorder with a p value of < 0.0001.

The study has divided the subjects into three groups :

Normal, those with metabolic syndrome, those with diabetes based on the concentration of inflammatory markers. As the concentration of inflammatory markers raised the percentage predicted values of pulmonary function tests reduced. The mechanism behind reduced lung function and metabolic syndrome might be attributed to obesity and inflammation resulting from it.[119]The limitation of the study is that it has not provided any data for the inflammatory markers.

A study conducted by Mahmoud M suggests that abundant connective tissue in lungs can make it a target site for damage in diabetic patients. In this the diabetic group was subdivided into two groups that is with those having HbA1c < 7(group II A) and the other group with HbA1c >7(group II B) and the group I were controls. Then comparison between pulmonary functions of the control and diabetic group was done which showed a significant difference in FEV_1, FEV_1/FVC, FEF 25-75% with a p value <0.05. But the difference was not significant for MVV. Comparison between group I and group IIA showed reduction in all PFTs' except FEF25-75 and MVV.Then comparison between group I and II B, between group II A and II B shows significant reduction in all parameters.Thus the study says that lung function is markedly reduced in diabetics when compared to normoglycemics.The limitation of this study is that it has not mentioned any criteria based how the diabetics were divided into those under control based on HbA1c values.**(120)**

A study done by Yamini et al. [121]showed obstructive, restrictive as well as mixed pattern of lung dysfunction in diabetic individuals. In this study comparison was done between males and females also. This study includes 25 healthy and 25 diabetic subjects.

Of this:

1.All females showed FVC < 80% of predicted values but among males only 48% showed FVC < 80%.

2.About 33% of women showed FEV1/FVC <70% where as 61% of males showed < 70%.

3. Thus altogether 54% of males showed obstructive pattern as indicated by FEV1/FVC < 70% and 31% showed restrictive pattern.

4. 67% of women had restrictive pattern.

5. Mixed pattern was seen in 33% women and one male.

Totally among diabetics 48% showed restrictive pattern and 28% showed obstructive pattern 20% had mixed pattern. The limitation of the study is that it did not mention about BMI which is an important confounding factor.

CONSEQUENCES OF REDUCED PULMONARY FUNCTIONS IN DIABETIC PATIENTS:

- Studies have reported an association between reduced lung function and death. In diabetic subjects 10% fall in FEV1 was linked to 12% increase in mortality rate.[131]

- The reduction in pulmonary function can reduce the threshold for clinical manifestations of lung diseases. Diabetic patients with reduced lung functions who develop pneumonia are more prone for developing complications at an early stage and the mortality rate is also high.[122]

- As collagen and elastin is widely distributed in the muscles, parenchyma of lungs and pleura, most part of the respiratory apparatus seems to be affected due to non-enzymatic glycosylation. This leads to increase in stiffness of lungs. Increase in stiffness can cause poor negative pressure pump. The compliance of lungs ultimately decreases. This leads to restrictive abnormality.Initially the patient may not appreciate the weakness of respiratory muscles. This may be because the workload during normal tidal breathing is put on the diaphragm than other respiratory muscles. But in due course of time these muscles will lose force generating ability. This in turn will increase the susceptibility of these people to

develop obstructive parameters. This depends on their sensitivity to various infections and pollutions. [70]

- ❖ As diabetic subjects are immunosuppresed, they develop defects in neutrophil functions. The process of phagocytosis, chemotaxis and bactericidal activities will be impaired in such subjects due to hyperglycemia. Hence these people are prone for developing infections.

- ❖ Apart from this the lung functions are deteriorated in diabetic subjects. This will add on to the risk of hospitalization in these subjects due to infections like pneumonia[123]Diabetic subjects with poor lung function are prone to develop myocardial infarction.[124]

- ❖ MECHANISM:

  Thickening of basement membrane of alveoli and pulmonary capillaries due to glycosylation can cause poor gas exchange across the respiratory membrane. This can ultimately lead to poor oxygenation of blood. In a person with already compromised coronary circulation, this type of pulmonary dysfunction can lead on to myocardial ischemia.

A study by Tibbilin et al. showed that in those with reduced peak expiratory flow rate, the proportion of mortality from coronary heart disease was more among male population in Sweden and Goteberg.[124]

Apart from this when a diabetic person with poor pulmonary function is taken for coronary artery bypass surgery, then his poor ventilatory function would interfere with weaning from ventilation.

The person will be prone to develop dyspnea owing to poor mechanical function of lungs, due to glycosylation of the scleroproteins.

DECREASED LUNG FUNCTION – A MARKER OF CARDIOVASCULAR DISEASE:

It is a known fact that failure of ventricles can lead to engorgement of lung vasculature and can cause edema of the interstitium. This will cause a drastic fall in the compliance of the lungs and will alter the lung volumes.

This reduced lung function acts as a marker for heart disease and studies have suggested that lung function should be carried out to predict the prognostic significance of ventricular arrhythmia.

This is because the increased rate of death and myocardial infarction which was associated with arrhythmia was confined to males with low percentage predicted values of FEV1 and low value of FEV/VC ratio.

MATERIALS AND METHODOLOGY

SETTING:

PLACE OF STUDY:

This case-control study was done in the Department of respiratory medicine, Department of Biochemistry at PSG Institute of Medical Sciences And Research Coimbatore, Tamilnadu, India.

The study was approved by the institutional ethics committee.

STUDY DESIGN:

This is a case control study. Patients with diabetes mellitus were selected for studying the abnormalities in pulmonary function and their pulmonary function test findings were compared with age and body mass index (BMI) matched controls.

The cases were those with uncontrolled blood sugar level within the age group of 30 – 60 years. The cases were selected from the out-patient department (OPD) of Endocrinology, provided they fulfilled the inclusion criteria. Then the cases and controls were subjected to pulmonary function tests.

TIME FRAME:

The study was conducted for one year that is from 1st May 2015 to 31st May 2016.

INCLUSION CRITERIA:

- Thirty diabetic subjects, whose fasting blood glucose was ≥ 126 mg/dl, two hour post prandial blood glucose was ≥ 200mg and HbA1c ≥ 6.5g% according to current WHO recommendations for the diagnostic criteria for diabetes and intermediate hyperglycemia[19] were enrolled in the study as cases.
- Participants were both men and women of age 30 – 60 years were included in the study.
- Thirty age and BMI matched normoglycemic healthy adults, with no clinical evidence of chronic illness or medication were enrolled in the control group.

EXCLUSION CRITERIA:

Patients with clinical evidence of any chronic respiratory illness like:

- Asthma
- Chronic obstructive pulmonary disease
- Tuberculosis

Patients with history of:

- Smoking
- occupational diseases
- Cardiac illness
- Connective tissue diseases
- Musculoskeletal disorders

Patients contraindicated for spirometry:

Absolute contraindications:

- Severe acute airflow limitation depicted by FEV_1 <50% of predicted.
- History of myocardial infarction or cerebrovascular accident in last 3 months.
- Uncontrolled hypertension: systolic blood pressure ≥200 mm Hg or diastolic pressure ≥120 mmHg.
- Known case of aortic aneurysm

Relative contraindications

- Moderate airflow limitation: FEV_1 <60% of predicted or <1.5 litres.
- Inability to perform spirometry of acceptable quality.
- Pregnancy, nursing mothers.

METHODOLOGY:

Informed written consent was obtained from all the participants before initiation of the study.

Detailed history of every participant was taken- regarding:

- Recent use of any anti diabetic medications.
- History of their behavioral habits such as smoking. Then all the smokers were excluded from the study.
- History of any acute or chronic illness was elicited to exclude them from the study provided they had a positive history.

LABORATORY COLLECTION:

BLOOD GLUCOSE ESTIMATION:

For fasting blood glucose measurement, about 2ml of blood sample was collected from the individual subjects after overnight fasting by venipuncture with the help of an evacuated tube system containing EDTA, at 8 a.m. in the morning.

Then the subjects were asked to take their normal diet (breakfast) and blood was collected for estimation of post prandial blood glucose two hours after food intake.

HbA1c was also measured from the blood collected for post prandial blood glucose estimation.

All blood samples were stored at 2 - 8º C after collection. Analysis of fasting blood glucose and post prandial blood glucose was done using COBAS INTEGRA 400/400 plus analyzer using glucose Hexokinase Gen.3(GLUC3) method. HbA1c was analysed using Bio-Rad laboratories, D-10 HbA1c version 220-0101 using Immuno-inhibition method.

BODY MASS INDEX:

Height and weight of all the participants were measured.

- ✓ Standing height was measured by asking the subject to stand bare foot with both the foot together against measuring instrument in centimeters.
- ✓ Weight was measured with weighing machine in light weight garments without foot wears in kg.

Then BMI was calculated for all the participants

- ✓ BMI was calculated using formula:

Weight in kg / (Height in meter) ^{2}.

SPIROMETRY:

The instrument used for measuring lung function was Pesomedicare smart spirometer. This is a personal computer based USB spirometer. This gives a precise value for spirometric measurement.

The instrument works on modern electronics, which fulfills all the requirements and guidelines of American Thoracic society (ATS) and European Respiratory society (ERS).

Features of software installed:

- GLI 2012, actual predicted.

  This covers different age, multiple ethinic reference values for spirometry. A set of predicted values for age, height and sex were derived using prediction equations. New regression equations were derived based on these values.

- SQL Data base: This data base makes sure that the datas are stored with high security. This uses applications that allow multiple user networks.

- This instrument can be upgraded any time.
- Back up facility is available, which is automated.
- The result can be obtained in a printed format.
- Linear flow sensor

This instrument makes use of complete linear flow sensor. The sensor is based on pneumotachograph . This helps to carry out the spirometric tests with high precision. The sensor are available with different orifice and negligible dead space. The measurements are not affected by humidity.

The system uses standard USB 2.0 interphase.

Pre-test advice to the participants:

All the participants were asked to:

1. Avoid heavy meal prior to the test.
2. Avoid strenuous exercise before the test.
3. Avoid tight clothing during the procedure.

The apparatus was properly caliberated. The operating technique of the instrument was based on its manual and the guidelines provided by The American Thoracic Society.[20]

- Then all the participants were given a prior explanation regarding the maneuver. A demo was shown to them. The test was carried out by a well trained personnel.
- The test was performed in the sitting posture with the participants' nose closed with a soft nose clip.

- All the participants were asked to perform the test three times with a period of fifteen minutes rest in between.
- While measuring forced vital capacity the subject was asked to give a maximum effort at the beginning of each blow. The subject was encouraged to blow out for at least six seconds and stop when the volume does not change for one second.

- Then the difference between the two largest forced vital capacity and forced expiratory volume at first second were analyzed and was found to be within 200ml.
- Best of the three measurements was taken into account.
- The highest value of forced vital capacity and forced expiratory volume at first second was used to calculate their ratio. The ratio expressed was as percentage of FVC.
- The parameters used for analysis were:

✓ Forced vital capacity(FVC)

✓ Forced expiratory volume at first second(FEV1)

✓ FEV1/FVC

✓ FEF25-75

✓ Peak expiratory flow rate(PEFR)The percentage predicted values of the above parameters were used for analysis purpose.

- For the FEV1/FVC, absolute ratio was taken.

STATISTICAL ANALYSIS:

- Statistical analysis was done using IBM SPSS statistics software (Statistical package for the social science version 19).
- Student 't' test was applied to compare the means of quantitative datas' like FEV1/FVC, FVC, FEV1, FEF25-75, PEFR.

- All values were expressed as mean ± SD (Standard deviation). The "p" values were interpreted as :

  (i) $p > 0.05$ was considered not significant.

  (ii) $p < 0.05$ was considered statistically significant.

- Correlation between pulmonary function test parameters like FEV1/FVC, FVC, FEV1, FEF25-75, PEFR with HbA1c and Body-Mass Index among the diabetics were analyzed by using Pearson correlation analysis.

RESULTS

Table 1:

Table 1 shows the physical parameters of the diabetic subjects as well as the normal healthy controls.

Both the groups were matched for age and body mass index. That is there was no statistical difference between the two groups as the “p” value was > 0.05.

The mean value of age for normal healthy controls was 42.63 ± 5.06 and for diabetic individuals it was 44.23 ± 5.96. Both the groups were matched for age. There was no statistical difference for the mean age for both the groups as the “p” value was 0.267 which was statistically not significant.

The mean value of body mass index for normal healthy controls was 26.70 ± 3.95 and for diabetic individuals it was 26.74 ± 4.18. Both the groups were matched for the body mass index. There was no statistical difference for the mean of body mass index for both the groups as the “p” value was 0.965 which was statistically insignificant.

Table 2:

Table 2 shows the comparison of pulmonary function tests between diabetic subjects and normal healthy controls.

The mean of FEV_1/FVC ratio for normal healthy individuals was 82.92 ± 4.81 and for the diabetic subjects it was 83.67 ± 5.96. There was no statistical difference between the two groups for the ratio of FEV_1 to FVC as the “p” value was 0.597.

The mean value of FVC for normal healthy controls was 99.90 ± 15.85 and for diabetic subjects it was 81.83 ± 18.11. There was statistically significant difference for the mean of forced vital capacity between the two groups as the “p” value was 0.000.

The mean value of FEV_1 for normal healthy controls was 91.53 ± 10.60 and for diabetic subjects it was 77.03 ± 13.81. The difference was statistically significant as the “p” was 0.000.

The mean value of PEFR for controls was 95.77 ± 15.54 and for the diabetic subjects it was 85.57 ± 18.69. There was statistically significant difference between the mean values of PEFR between the two groups, as the “p” value was 0.025.

The mean value of $FEF_{25-75\ \%}$ for normal healthy controls was 74.83 ± 20.36 and for diabetic individuals it was 66.90 ± 24.5. The difference was not statistically significant as the “p” value was 0.179.

This study shows that the pulmonary function parameters like FVC, FEV1 and PEFR are reduced in participants with type 2 diabetes as when compared to normal healthy participants.

The mean of both FEV_1/FVC ratio and $FEF_{25-75\%}$ between the normal healthy controls and diabetic individuals was not statistically significant as their “p” value was greater than 0.05.

Table 3 :

Table 3 shows comparison of pulmonary function tests among diabetic subjects with HbA_1c <7 and HbA_1c > 7.

The 30 diabetic subjects were divided into two groups:

Group 1 = Diabetic subjects with HbA_1c < 7 g%

Group 2 = Diabetic subjects with HbA_1c > 7 g%

The mean of FEV_1/FVC in diabetic subjects with HbA_1c < 7 g% was 82.92 ± 5.12 and in those with HbA_1c > 7 g%, it was 84.10 ± 6.49. But the difference of the mean values between the two groups was not statistically significant as the “p” value was 0.611.

The mean value of FVC in diabetic individuals with HbA_1c < 7 g% was 88.64 ± 21.50 and for those with HbA_1c >7g% was 77.89 ± 15.07. This difference was also not statistically significant as the “p” value was 0 .119.

The mean value of FEV_1 for diabetic individuals with HbA1c < 7 g % was 80.91 ± 14.21 and for those with HbA_1c >7g% was 74.79 ± 13.43. This also showed no statistical difference between the two groups as the “p” value was 0.249.

The mean value of $FEF_{25-75\%}$ for diabetic individuals with HbA_1c < 7 g% was 68.18 ± 22.63 and for those with HbA_1c >7g%, it was66.16 ± 26.20. This was also not statistically significant as the “p” value was 0.214.

The mean value of PEFR in diabetic subjects with HbA_1c < 7g % was 91.45 ± 12.04 and for those with HbA_1c > 7g%, it was 82.16 ± 21.19.

Thus the various parameters of pulmonary function tests showed no significant difference between the diabetic subjects with HbA_1c < 7 g% and HbA_1c > 7 g%.

Table 4 :

Table 4 shows the Pearson correlation of pulmonary function tests and glycosylated hemoglobin among diabetic subjects.

Pearson correlation (r^2) for FEV_1/FVC and HbA_1c was 0.307 among diabetic subjects. This showed no correlation as the “p” value was 0.09.

Pearson correlation (r^2) for FVC and HbA_1c was -0.202 among diabetic subjects. This showed no correlation as the “p” value was 0.284.

Pearson correlation (r^2) for FEV_1 and HbA_1c was -0.011 among diabetic subjects. This showed no correlation as the “p” value was 0.954.

Pearson correlation (r^2) for $FEF_{25-75\ \%}$ and HbA1c was .136 among diabetic subjects. This showed no correlation as the “p” value was 0.473.

Pearson correlation (r^2) for PEFR and HbA_1c was .023 among diabetic subjects. This showed no correlation as the “p” value was 0.904.

There was a slight negative correlation between FVC, FEV1 and HbA_1c. But this was not statistically significant.

Table 5 :

Table 5 shows Pearson correlation between pulmonary function tests and body mass index among participants:

Pearson correlation (r^2) for FEV_1/FVC and BMI among the participants was 0.114. This showed no correlation as the “p” value was .385.

Pearson correlation (r^2) for FVC and BMI among the participants was -0.041. This showed no correlation as the “p” value was 0.756.

Pearson correlation (r^2) for FEV_1 and BMI among the participants was -0.019. This showed no correlation as the “p” value was 0.884.

Pearson correlation (r^2) for $FEF_{25-75\ \%}$ and BMI among all the participants was 0.016. This showed no correlation as the “p” value was 0.905.

Pearson correlation (r^2) for PEFR and BMI among all the participants was 0.017. This showed no correlation as the “p” value was 0.899.

There was a slight negative correlation between FVC, FEV_1 and BMI, but this was again not statistically significant.

Table 6 :

Table 6 shows the correlation between pulmonary function tests and body mass index among diabetic subjects.

This was done to confirm whether the body mass index had any correlation with pulmonary function tests among the diabetic individuals whose lung function was already compromised.

Among diabetic subjects the Pearson correlation for FEV_1/FVC and BMI was 0.259 with a “p” value of 0.167. This correlation showed no significance.

Pearson correlation for FVC was -0.077 with a “p” value of 0.688.

Pearson correlation for FEV_1 was -0.018 with a p value of 0.927.

Pearson correlation for $FEF_{25-75\ \%}$ was 0.106 with a “p” value of 0.578.

Pearson correlation for PEFR was 0.098 with a “p” value of 0.606.

This showed a slight negative correlation between FVC, FEV_1 and BMI among the diabetic subjects. But this correlation was not statistically significant.

Table 7 :

Table 7 shows comparison of pulmonary function tests between participants with BMI < 25 and BMI > 25 among diabetic subjects:

Participants were categorized into two groups:

Group 1: BMI < 25

Group 2: BMI > 25

The mean values for the various parameters for both the groups were:

FEV_1/FVC for those with BMI<25 among the diabetic individuals was 83.61 ± 5.23 and for those with BMI >25 was 83.70 ± 6.37. This was not statistically significant as the “p” value was 0.971.

FVC for those with BMI < 25 among the diabetic individuals was 76.11 ± 12.11 and for those with BMI >25 was 84.28 ± 19.90. This was also not statistically significant as the “p” value was 0.265.

FEV1 for those with BMI < 25 among the diabetic individuals was 74.33 ± 12.83 and for those with BMI >25 was 78.19 ± 14.35. This difference was not statistically significant as the “p” value was 0.493.

$FEF_{25-75\ \%}$ for those with BMI < 25 among the diabetic individuals was 60.33 ± 17.93 and for those with BMI >25 was 69.71 ± 26.81. This showed no statistical significance as the “p” value was 0.347.

PEFR for those with BMI < 25 among the diabetic individuals was 85.33 ± 18.40 and for those with BMI >25 was 85.66 ± 19.26. This also showed no statistical significance as the “p” value was 0.965.

This study showed no significant difference in the mean values of pulmonary function tests in both groups.

TABLE 1:

PHYSICAL CHARACTERISTICS OF PARTICIPANTS

Parameters	Controls, (n=60) Mean ± SD	Patients with Dm (n=60) Mean ± SD	"P" VALUE	Significance
Age (Years)	42.63 ± 5.06	44.23 ± 5.96	0.267	NS(> 0.05)
BMI (kg/m^2)	26.70 ± 3.95	26.74 ± 4.18	0.965	NS(> 0.05)

DM: Diabetes mellitus

BMI: Body mass index

P < 0.05 – Significant

P > 0.05 – Not Significant (NS)

TABLE 2:

COMPARISON OF PULMONARY FUNTION TESTS BETWEEN DIABETIC SUBJECTS AND NORMAL HEALTHY CONTROLS.

Parameters: Percentage predicted values	Control subjects Mean ± SD	Diabetic subjects Mean ± SD	"p"value	Significance
FEV_1/FVC	82.92±4.81	83.67±5.96	0.597	NS (>0.05)
FVC	99.90±15.85	81.83±18.11	0.000	HS (<0.05) *
FEV_1	91.53±10.60	77.03±13.81	0.000	HS (<0.05) *
$FEF_{25-75\%}$	74.83±20.36	66.90 ± 24.57	0.179	NS (>0.05)
PEFR	95.77 ± 15.54	85.57 ± 18.69	.025	HS (<0.05) *

FVC – Forced vital capacity

FEV_1 – Forced expiratory volume at first second

FEF25-75% – Forced expiratory flow rate during first half of FVC

PEFR – Peak expiratory flow rate

$P < 0.05$ – Significant

$P > 0.05$ – Not Significant (NS)

TABLE 3:

COMPARISON OF PULMONARY FUNCTION TESTS IN DIABETIC SUBJECTS WITH HbA1c < 7 and HbA1c > 7.

Parameters: Percentage predicted values	Subjects with HbA1c<7 Mean ± SD	Subjects with Hba1c>7 Mean ± SD	"p"value	Significance
FEV_1/FVC	82.92±5.12	84.10±6.49	0.611	NS (>0.05)
FVC	88.64 ±21.50	77.89±15.07	0.119	NS (>0.05)
FEV_1	80.91±14.21	74.79 ±13.43	0.249	NS (>0.05)
$FEF_{25-75\%}$	68.18±22.63	66.16 ± 26.20	0.214	NS (>0.05)
PEFR	91.45 ± 12.04	82.16 ± 21.19	1.330	NS (>0.05)

HbA1c – Glycosylated hemoglobin

P < 0.05 – Significant

P > 0.05 – Not Significant (NS)

TABLE 4:

PEARSON CORRELATION OF PULMONARY FUNCTION TESTS AND GLYCOSYLATED HEMOGLOBIN AMONG DIABETIC SUBJECTS:

PARAMETERS % predicted value	r^2 (Pearson correlation)	"p" VALUE	SIGNIFICANCE
FEV1/FVC with HbA1c	0.307	0.098	NS (>0.05)
FVC with HbA1c	-0.202	0.284	NS (>0.05)
FEV_1 with HbA1c	-0.011	0.954	NS (>0.05)
FEF_{25-75} with HbA1c	0.136	0.473	NS (>0.05)
PEFR with HbA1c	0.023	0.904	NS (>0.05)

r^2 – Pearson correlation

HbA1c – Glycosylated hemoglobin

P < 0.05 – Significant

P> 0.05 – Not Significant (NS)

TABLE : 5

PEARSON CORRELATION FOR BODY MASS AND INDEX PULMONARY FUNCTION TESTS AMONG THE PARTICIPANTS:

Parameters % predicted value	r^2 (PEARSON CORRELATION)	"p" value	Significance
FEV1/FVC with BMI	0.114	0.385	NS (>0.05)
FVC with BMI	-0.041	0.756	NS (>0.05)
FEV_1 with BMI	-0.019	0.884	NS (>0.05)
FEF_{25-75} with BMI	0.016	0.905	NS (>0.05)
PEFR with BMI	0.017	0.899	NS (>0.05)

$P < 0.05$ – Significant

$P > 0.05$ – Not Significant (NS)

TABLE : 6

PEARSON CORRELATION FOR BODY MASS INDEX AND PULMONARY FUNCTION TESTS AMONG DIABETIC INDIVIDUALS:

Parameters % predicted value	r^2 (PEARSON CORRELATION)	"p"value	Significance
FEV1/FVC with BMI	0.259	0.167	NS (>0.05)
FVC with BMI	-0.077	0.688	NS (>0.05)
FEV_1 with BMI	-0.018	0.927	NS (>0.05)
FEF_{25-75} with BMI	0.106	0.578	NS (>0.05)
PEFR with BMI	0.098	0.606	NS (>0.05)

P < 0.05 – Significant

P > 0.05 – Not Significant (NS)

TABLE 7:

COMPARISON OF PULMONARY FUNCTION TESTS BETWEEN PARTICIPANTS WITH BMI < 25 AND > 25 AMONG DIABETIC SUBJECTS:

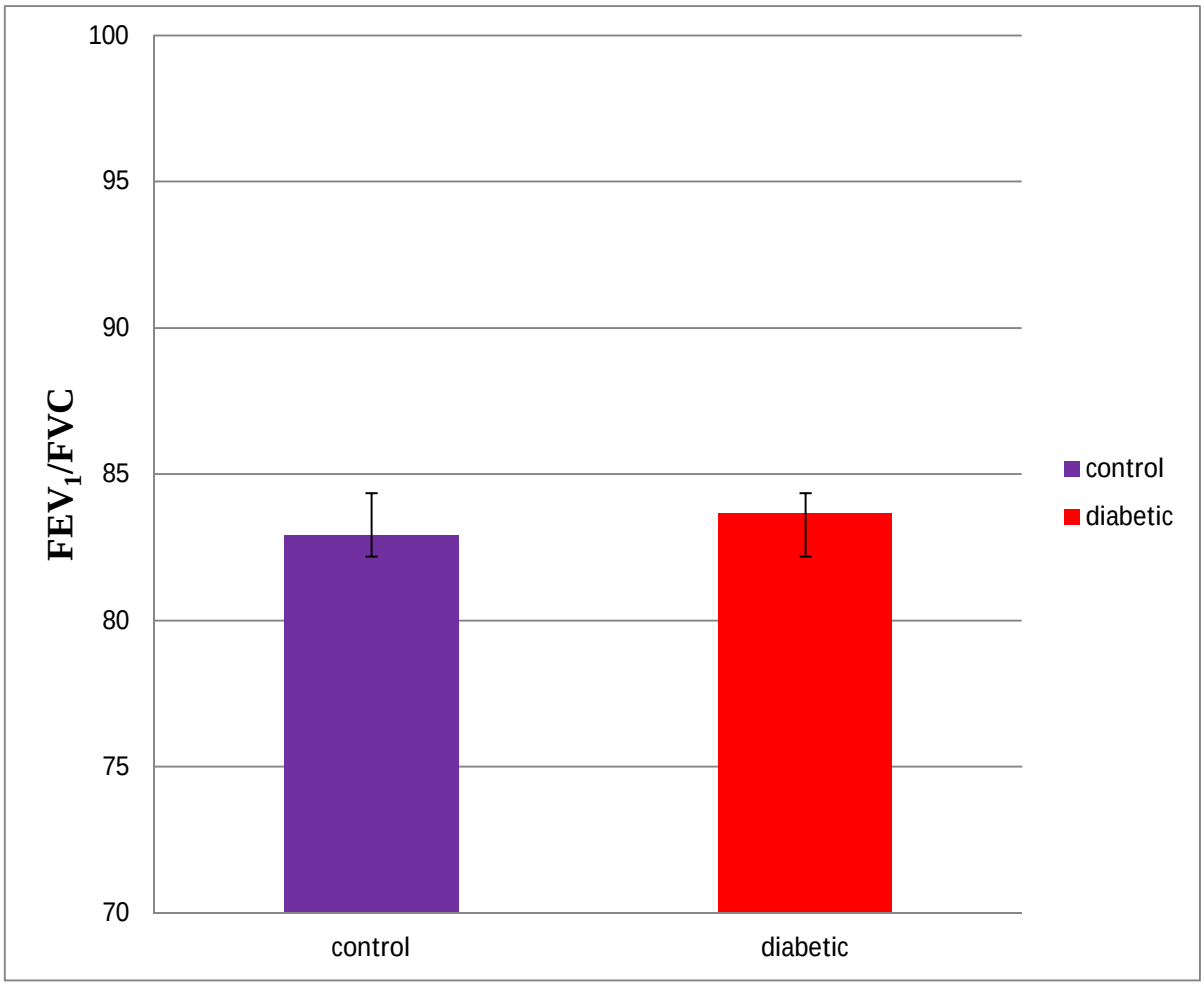
PARAMETERS: Percentage Predicted values	SUBJECTS WITH BMI<25 Mean ± SD	SUBJECTS WITH BMI>25 Mean ± SD	"p" VALUE	SIGNIFICANCE
FEV1/FVC	83.61±5.23	83.70±6.37	.971	NS (>0.05)
FVC	76.11 ±12.11	84.28±19.90	.265	NS (>0.05)
FEV1	74.33±12.83	78.19±14.35	.493	NS (>0.05)
$FEF_{25-75\%}$	60.33±17.93	69.71 ± 26.81	.347	NS (>0.05)
PEFR	85.33 ± 18.40	85.66 ± 19.26	.965	NS (>0.05)

P < 0.05 – Significant

P > 0.05 – Not Significant (NS)

CHART 1:

COMPARISON OF FEV_1/FVC BETWEEN DIABETIC SUBJECTS AND NORMAL HEALTHY CONTROLS. (MEAN & SD)

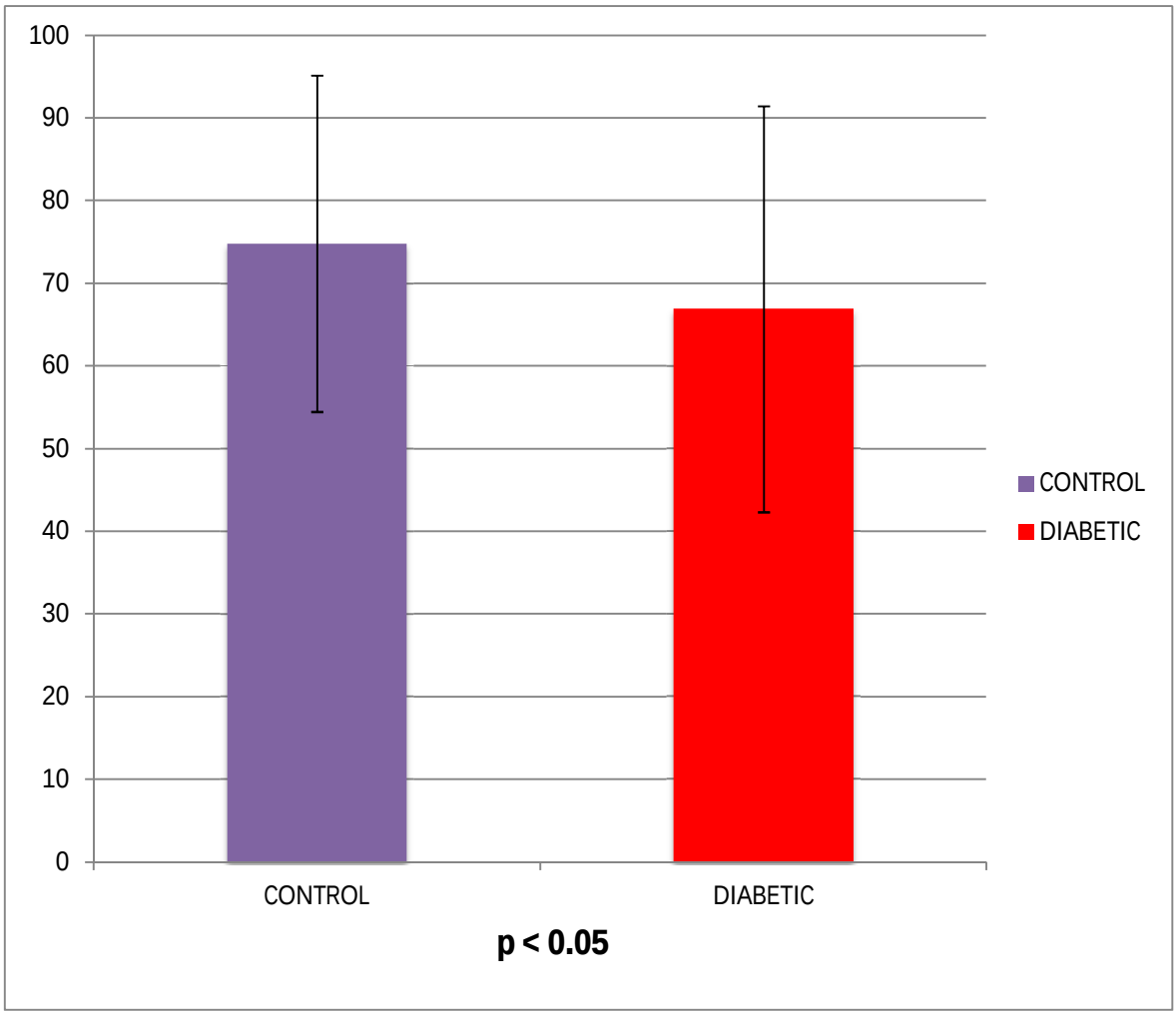


FEV_1 – Forced expiratory volume at first second.

FVC – Forced vital capacity

CHART 2:

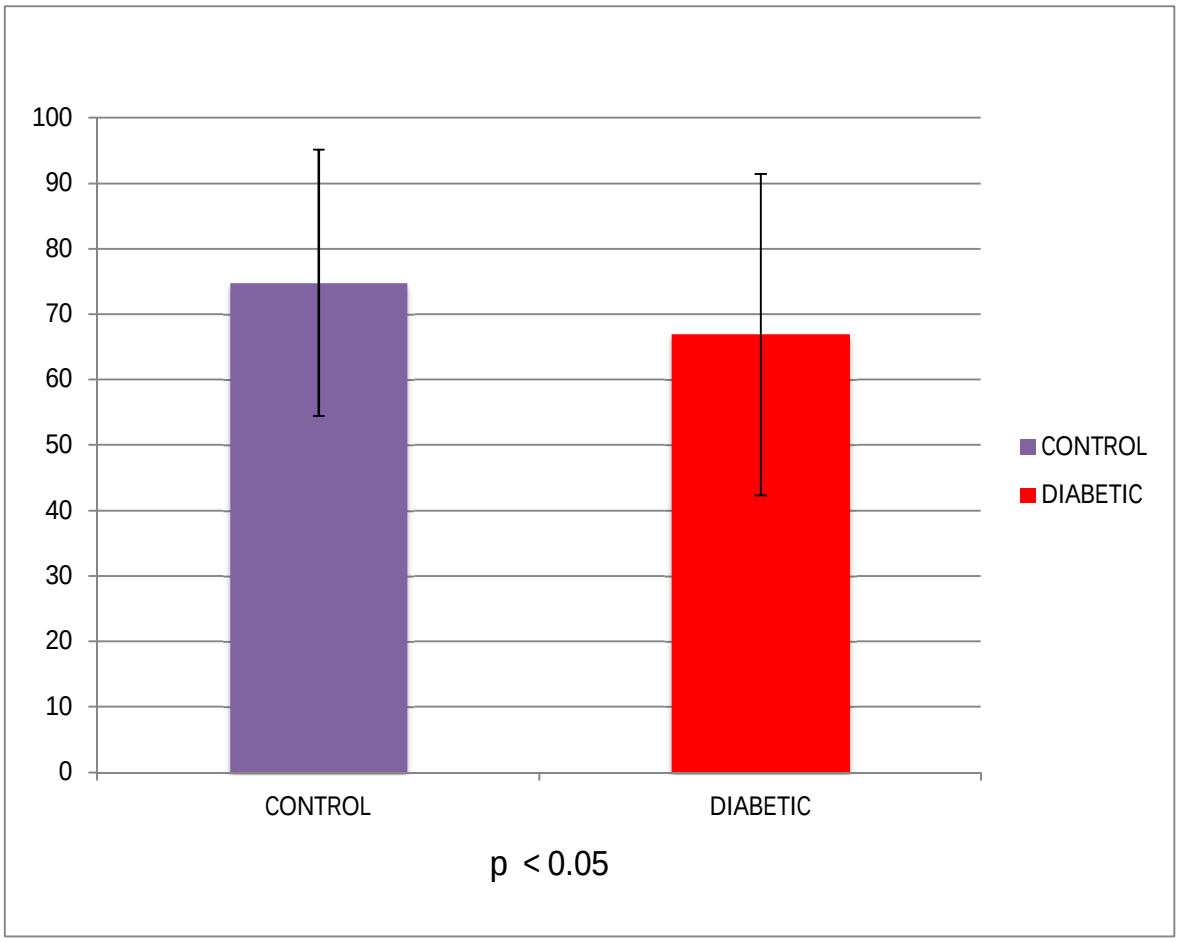
COMPARISON OF FVC BETWEEN DIABETIC SUBJECTS AND NORMAL HEALTHY CONTROLS.



FVC – Forced vital capacity

CHART 3 :

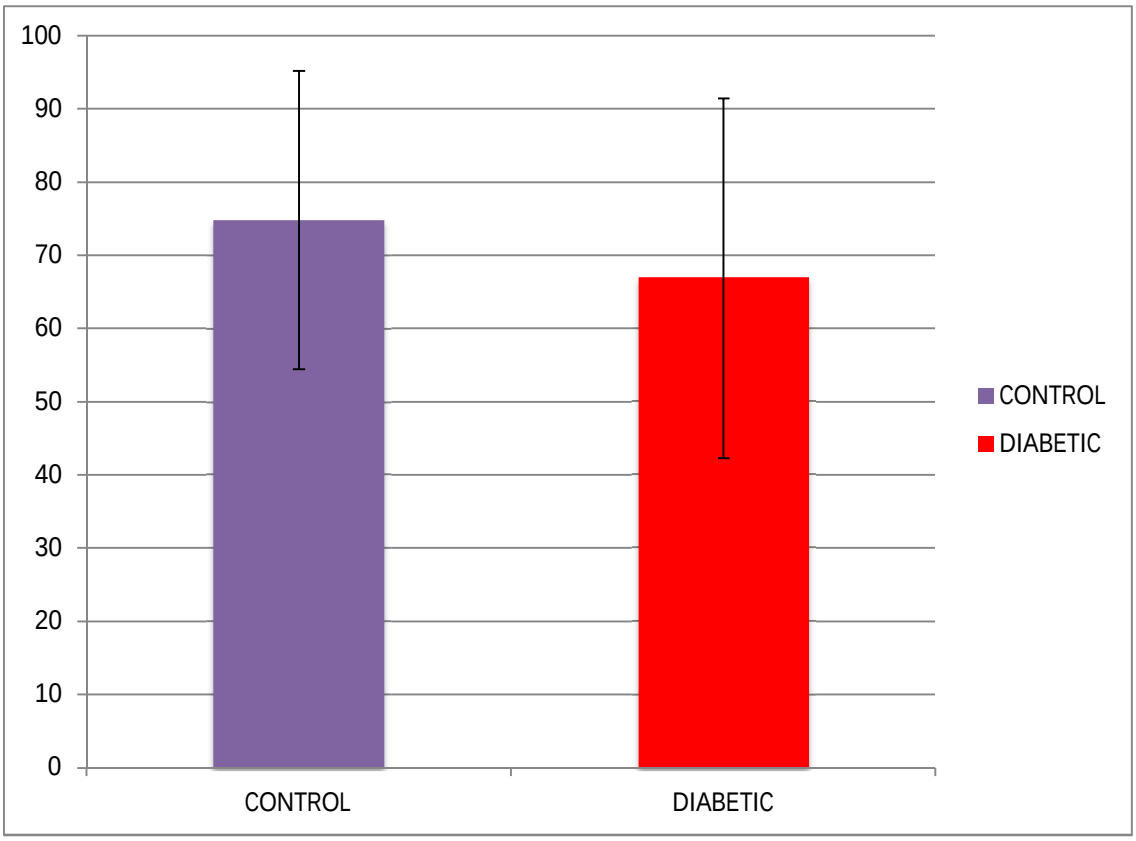
COMPARISON OF FEV_1 BETWEEN DIABETIC SUBJECTS AND NORMAL HEALTHY CONTROLS.



FEV_1 – Forced expiratory volume at first second

CHART 4 :

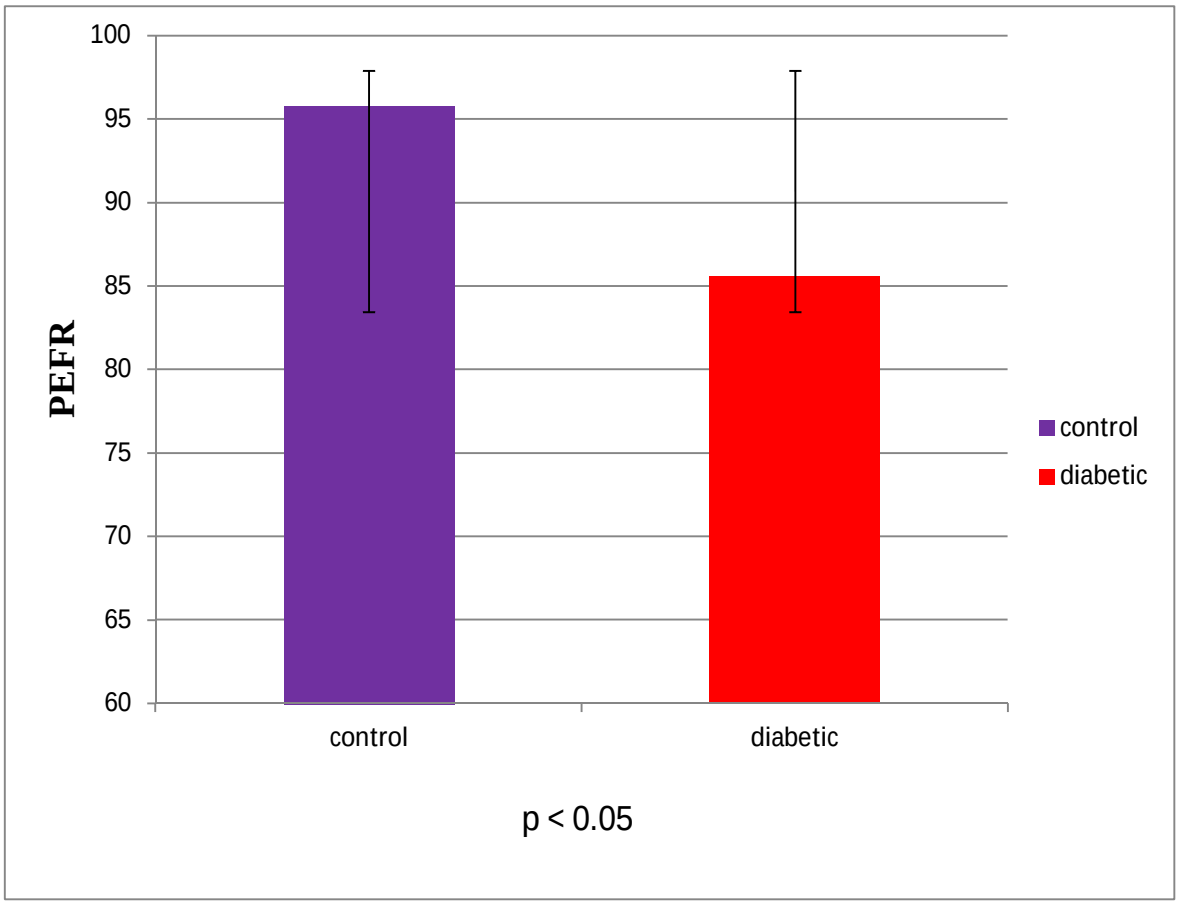
COMPARISON OF $FEF_{25-75\%}$ BETWEEN DIABETIC SUBJECTS AND NORMAL HEALTHY CONTROLS.



$FEF_{25-75\%}$ -Forced expiratory flow rate at 25-75% of FVC.

CHART 5:

COMPARISON OF PEFR BETWEEN DIABETIC SUBJECTS AND NORMAL HEALTHY CONTROLS.



PEFR – Peak expiratory flow rate

DISCUSSION

Lung parenchyma which includes the respiratory bronchioles, alveolar ducts, alveoli, blood vessels, interstitium are rich in connective tissue elements such as collagen and elastin.

Though the bronchioles lack cartilages the lungs are able to maintain their patency because of the elasticity of its parenchyma. The major determinant of the elasticity of the lung parenchyma is elastin fibers. The stretching ability of the elastin fibers are about 140% of their length in the relaxed state.[54]The elastin fibers with few fibroblast are found in the alveoli of lungs which promotes normal exhalation.

But collagen which is inelastic, contributes to the architecture and tensile strength of the lung. Collagen can stretch only up to 2% of its resting length.

The elastic connective tissue surrounding the alveoli of lungs gets stretched during inhalation. During the process of expiration these fibers recoil to squeeze the air out. Thus expiration is a passive process where there is neither need of any work to be done nor there is any energy expenditure. This property is due to the normal elasticity of the lungs.

The interstium of lung parenchyma consists mainly of collagen fibers which are of mainly type 1 and type 3. Collagen is responsible for the structural framework of the alveolar wall that is, it maintains the architecture of alveolar wall.

In diabetic individuals there occurs non-enzymatic glycosylation of collagen and elastin, which in turn can affect the ventilator functions.

In this study the diabetic subjects and the controls were matched for age and body mass index. So both the confounding factors were excluded .

The ventilatory functions in this study which was measured by Pesomedicare smart spirometer showed the following data:

1. Forced vital capacity (FVC):

Forced vital capacity which is an important component of flow volume loop depicts the total volume of air that is exhaled with maximum effort.

The normal percentage predicted value of FVC is 80-120%.

This study shows a marked reduction in forced vital capacity in individuals with diabetes as when compared to normal healthy controls.

The reason attributable to this reduction may be due to:

- Reduced compliance of lungs due to due to non-enzymatic glycosylation of collagen and elastin.
- The other reason must be thickening of the basal lamina of the epithelium in the alveoli.

This result goes hand in hand with many other studies.

A cohort study conducted by Davis et al. [(72)] among the European community shows similar decrease in forced vital capacity. The study states that the reduced value of forced vital capacity is due to glycation of proteins in diabetic individuals which will affect the compliance of lungs. Chronic exposure

to high glucose level can lead to thickening of alveolar basement membrane. These pathologic changes in diabetic individuals were identified by the histologic changes found in the lung of diseased.

A cross sectional study done by Lange P et al. [89] among adults of middle age in United states also showed a marked decrease FVC in diabetic subjects. The study says that the reduction in FVC among diabetic population is faster as when compared to non- diabetic population with a difference of approximately 8%. Apart from the non enzymatic glycosylation of proteins of the bronchial tree and microangiopathy the study includes another factor. That is, inflammation and oxidative stress among the diabetic subjects can affect the efficiency of respiratory muscles, which in-turn can affect ventilation.

A study done by Asanuma et al. [122] among diabetic subjects of Pakistan showed marked decrease in FVC. The study says that this one of chronic complications of diabetes owing to poor recoiling of lungs as a result of glycation of scleroproteins.

A study by Barrett et al. [123] says that the reduction in FVC among diabetic population implies that these effects of hyperglycemia actually develops even before the person becomes full blown diabetic suggesting that even the impaired glucose tolerance state can lead to structural and functional abnormality of structural proteins owing to non enzymatic glycosylation.

A study by Marvisi M et al. [124] shows that there is reduction in FVC among diabetic subjects which is attributable to the fact that hyperglycemic state

can lead to thickening of basement membrane of alveoli and pulmonary capillaries. The study also suggests a decrease in the diffusing capacity of lungs as the DL_{CO} value was markedly reduced in diabetic subjects due to thickening of basal lamina of pulmonary capillaries.

2. Forced expiratory volume at first second (FEV_1):

It is the amount of air breathed out with maximum effort in the first second. The normal percentage predicted value of FVC is 80-120%.

This study shows a marked reduction in FEV_1 among diabetic population as when compared to normal healthy controls.

The reason for marked reduction in FEV1 is attributed to:

- Poor recoiling of lung tissues due to non-enzymatic glycosylation of the scleroproteins collagen and elastin.
- Thickening of basal lamina of alveolar epithelium.

This result correlates with the following studies.

A cohort study conducted by Davis et al. [72] and a study by Sanjeev sinha et al.[102] suggests that the reduction of FEV_1 among the diabetic subjects when compared to normal healthy controls is due to poor elastic recoiling of the lungs as the visco elastic nature of lung parenchyma is lost as a result of thickening of collagen and loss of elastic nature of elastin owing to glycation.

3. Peak expiratory flow rate (PEFR):

The normal value of PEFR is 400-600ml/min.This study shows that in diabetic subjects there is marked reduction in the PEFR values as compared to the

normal subjects. This implies that there is marked fall in the strength of the muscles of expiration, which is reflected as fall in force generating capacity of these muscles. This may be either due to increased protein catabolism or due to poor neuromuscular function of respiratory muscles as a part of diabetic neuropathy or change in composition of muscle fibers.

This result is similar to the study done by Kabitz HJ et al. [125] which states that the reduction in peak expiratory flow rate among diabetic subjects is due to poor efficiency of muscles of expiration , as the maximum velocity with which air is forced out of lungs depends on the strength of muscles of expiration. This may be due to enhanced protein catabolism.

A study done by Marin P et al. [125] also shows a marked reduction in peak expiratory flow rate in diabetic subjects as when compared to normal healthy controls. This is attributed to the fact that, in diabetic individuals' peripheral neuropathy can result in reduced neuromuscular function, which can affect the muscles of respiration.

4. FEV_1/ FVC :

In this study the mean of absolute ratio of FEV_1 to FVC among diabetics were found to be slightly more than that of the normal controls but was not statistically significant.

The increase in the mean value of the ratio suggests that diabetic individuals have a restrictive pattern of lung disease.

This result correlates with certain other studies.

A study by Barrett et al. [123] says that the increase in FEV_1 / FVC that is more than 0.70 among diabetic subjects supports the evidence of restriction according to the guidelines given by the American thoracic society and European respiratory society.

5. $FEF_{25-75\%}$:

This exhibits forced expiratory flow somewhere at the middle of forced vital capacity.

This value exhibits the patency of small airways which actually depends on the total volume of air exhaled that is forced vital capacity.

The mean value of forced expiratory flow at $_{25-75\%}$ is roughly reduced in diabetic subjects than that of the controls. But this value is not statistically significant. This again depends on the mechanical properties of lungs.

This result is in accordance with the study done by Sodhi C et al.[74]

The study says that $FEF_{25-75\%}$ is said to depend on both the neuromuscular factors as well as the mechanical properties of the respiratory system as FEF25-75% depicts nothing but the initial part of forced vital capacity.

According to the guidelines given by the American Thoracic Society FEV1/FVC $\geq$ 70% with markedly reduced value of FVC and FEV1 values suggest restrictive type of respiratory impairment.[10]In this study the mean of percentage predicted values of forced vital capacity as well as forced expiratory volume at

first second is markedly reduced in diabetic subjects when compared to normal subjects. Hence the diabetic subjects in this study show a restrictive pattern of ventilatory impairment.

Studies have shown low vital capacity and restrictive pattern of respiratory impairment among type 2 diabetic subjects.[128,129]

6. Comparison of pulmonary functions in diabetic subjects with $HbA_1c < 7g\ \%$ and $HbA_1c > 7g\ \%$.

A study by Van den Borst et al. showed a restrictive pattern of lung function among diabetic subjects which was statistically significant. But the limitation of the study was that it did not take BMI, HbA1c and smoking into consideration. [130]The present study has compared the pulmonary functions with the glycemic control. A good indicator for glycemic control is HbA1c value.

The correlation of HbA1c of diabetic subjects with their pulmonary function tests' showed slightly negative correlation for FVC and FEV1.But this was not statistically significant. The slight negative correlation shows that lung function is slightly decreased in diabetic subjects as the lung parenchyma which is rich in collagen and elastin is prone for non-enzymatic glycosylation due to high blood glucose level. This can lead to stiffening of parenchyma, which will ultimately affect the lung volumes and capacities.

The lung parenchyma changes are evident by electron microscopic studies of lung tissue of diseased diabetic subjects. It showed thickening of capillary endothelium and basement membrane.

The statictiscal insignificance may be due to the fact that, though HbA1c levels are strong indicators of glycemic control, it depicts the glycemic control for only a short duration of 1-3 months. And this short term control in no way can explain the effect of long term high plasma glucose level on lung mechanics.

This correlates with the study done by Lange P et al. [110] This study was done in The United nations among the middle aged population. The HbA_1c values showed a negative correlation with lung functions as high blood glucose will affect the mechanical function of lungs.

7. **Correlation of body mass index with pulmonary functions among diabetic individuals:**

The correlation between body mass index and pulmonary function tests' among diabetic subjects showed a slight negative correlation for both forced vital capacity and forced expiratory volume at first second. But this was not statistically significant. This may be attributed to small sample size.

This result goes hand in hand with the study conducted by Jitendra Singh et al.[86]which shows that there is no correlation between pulmonary function tests and factors like body mass index and gender.

CONCLUSION

In diabetic patients following changes are noted in the lung:

- Non-enzymatic glycosylation of collagen and elastin can lead to increased cross link formation between polypeptides of collagen causing stiffening of lung parenchyma as well as poor elastic recoiling of lung tissue. This causes restrictive pattern of lung dysfunction in these subjects.
- Microangiopathy not only affects the kidneys, nervous system, and eyes, but also damages the alveolar basement membrane.
- There is more chance for reduced strength of respiratory muscles, owing to increased protein catabolism.
- Next important complication in diabetes is thickening of basement membrane of thoracic and phrenic nerves as a part of diabetic neuropathy, which can cause demyelination, chromatolysis of their axons and Schwann cells. This can also lead to decrease in strength of respiratory muscles.

Thus spirometry a non-invasive procedure must be added as a part of investigation to monitor the effects of diabetes on lungs and also for early detection of lung function to prevent any further complication due to poor ventilatory function.

- A good control of blood sugar may decrease the risk of mortality through correction of ventilatory functions.
- In a person with uncontrolled blood sugar level the chance for developing respiratory infection is more. Hence it is advisable to immunize them against influenza and pnuemoccocus.[135]
- Studies say that pyridoxamine and aminoguanidine compounds have the ability to prevent the formation of advanced glycation end products, in animal models.[12]

Aminoguanidine is an AGE-inhibitor. It helps to prevent various signs of aging process. But as it has the ability to prevent or slow down the proteins from cross linking, it can be tried in diabetic subjects also.

Aminoguanidine tends to bind to the sugars and prevent the binding of sugars to the lysine group of proteins. Thus aminoguanidine helps to maintain and stabilize the glucose metabolism [136].

1. Stage 3 trial for aminoguanidine is going on at the Alteon Corporation in the USA. The main function of aminoquanidine, carnosine, acetyl-α-carnitine is to prevent cross link formation.
2. Another important development is ALT-711 (Thiazolium salt). This is under 2nd stage of trial. This helps to break the existing links.

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ANNEXURE – I

PSG Institute of Medical Science and Research, Coimbatore
Institutional Human Ethics Committee
INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS FOR CASES

I, **Dr.R.L.Bhavya**, am carrying out a study on the topic: **Pulmonary Functions In Type II Diabetes Patients And its correlation with factors affecting glycemic status** as part of my project being carried out under the aegis of the Department of Physiology

(*Applicable to students only*): My research guide is: **Prof.Nagashree.R.**

The justification for this study is:

Though pulmonary dysfunction in TypeII Diabetes patients is well documented in literature, yet there is lack of adequate data on Indian population, more so from southern India. The present study will attempt to fill the paucity of knowledge in Indian scenario.

The objectives of this study are:

Primary Objectives:

- **To assess the pulmonary functions of TypeII Diabetic patients and compare it with age and sex matched healthy individuals**

Secondary Objectives:

To identify the correlation between lung functions of Diabetic patients and factors like

- **Age**
- **Sex**
- **BMI**
- **HbA1c**

Sample size: 30 TypeII Diabetic participants and 30 normal study volunteers.

Study volunteers / participants are (specify population group & age group): **both sex, age matched**.

Location: Endocrinology clinic PSGIMS & R

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out:
Initial interview: **collecting participants(controls) details through data collection tools. The controls and cases will undergo pulmonary function testing, using Pesomedicare smart spirometer.** Data collected will be stored for a period of fifteen years. We will not use the data as part of another study.

Benefits from this study for the study volunteers?

- **To know pulmonary functions of the type II Diabetic patients.**
- **If they have abnormal PFT's they are informed and send to pulmonology or respiratory medicine department for further evaluation.**

Risks involved by participating in this study: **NO**

How the **results** will be used:

- **To my project study.**

If you are uncomfortable in answering any of our questions during the course of the interview, **you have the right to withdraw from the interview / study at anytime.** You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only. You will be informed about any significant new findings - including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature / Left thumb impression of the Study Volunteer / Legal Representative:

Signature of the Interviewer with date:

Witness:

Contact details of PI: Phone: : +91-0422-2570170 Extension No.: 5809.
PHONE 9715874362
rlbhavya83@gmail.com

Contact details of IHEC: Phone: +91-0422-2570170 Extension No.: 5818.

ANNEXURE – II

PSG Institute of Medical Science and Research, Coimbatore
Institutional Human Ethics Committee
INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS FOR CONTROLS

I, **Dr.R.L.Bhavya**, am carrying out a study on the topic: **Pulmonary Functions In TypeII Diabetic Patients And its correlation with factors affecting the glycemic status ,** as part of my project being carried out under the aegis of the Department of Physiology

(*Applicable to students only*): My research guide is: **Prof.Nagashree.R.**

The justification for this study is:

Though pulmonary dysfunction in Diabetic patients is well documented in literature, yet there is lack of adequate data on Indian population, more so from southern India. The present study will attempt to fill the paucity of knowledge in Indian scenario.

The objectives of this study are:

Primary Objectives:

- **To assess the pulmonary functions of TypeII Diabetic patients and compare it with age and sex matched healthy individuals**

Secondary Objectives:

To identify the correlation between lung functions of RA patients and factors like

- **Age**
- **sex**
- **BMI**
- **HbA1c**

Sample size: 30 TypeII Diabetic participants and 30 normal study volunteers.

Study volunteers / participants are (specify population group & age group): **both sex, age matched**.

Location: Endocrinology clinic PSGIMS & R

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out:
Initial interview : **collecting participants(controls) details through data collection tools. The controls and cases will undergo pulmonary function testing, Pesomedicare smart spirometer.** Data collected will be stored for a period of fifteen years. We will not use the data as part of another study.

Benefits from this study for the study volunteers?

- **To know pulmonary functions of the controls.**
- **If they have abnormal PFT's they are informed and send to pulmonology or respiratory medicine department for further evaluation.**

Risks involved by participating in this study: **NO**

How the **results** will be used:

- **To my project study.**

If you are uncomfortable in answering any of our questions during the course of the interview, **you have the right to withdraw from the interview / study at anytime.** You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only. You will be informed about any significant new findings - including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature / Left thumb impression of the Study Volunteer / Legal Representative:

Signature of the Interviewer with date:

Witness:

Contact details of PI: Phone: +91-0422-2570170 Extension No.: 5809.
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Contact details of IHEC: Phone: +91-0422-2570170 Extension No.: 5818.

ANNEXURE - III

பி.எஸ்.ஜி மருத்துவக்கல்லூரி கோயம்புத்தூர்

ஒப்புதல் படிவம்

டாக்டர் ரா.ல. பவ்யா ஆகிய நான் PSG மருத்துவக்கல்லூரியின் உடலியங்கயல் துறையின் கீழ் "சர்க்கரை நோயாளிகளுக்கு வரக்கூடிய நுரையீரல் பாதிப்புகளையும் மற்றும் உடம்பில் சர்க்கரையின் அளவை மாற்றக்கூடிய வேறுபல காரணயுக்திகளோடு ஒப்பிட்டு பார்த்தல்" என்ற தலைப்பில் ஆய்வு மேற்கொள்ள உள்ளேன்.

என் ஆய்வு வழிகாட்டி – டாக்டர் ர. நாகஸ்ரீ

ஆய்வு மேற்கொள்வதற்கான அடிப்படை

சர்க்கரை நோயால் நுரையீரலில் வரக்கூடிய பாதிப்புகளின் பற்றிய ஆய்வுகள் சில மட்டுமே உள்ளன மற்றும் இந்த பாதிப்புகள் அவர்களின் தினசரி வாழ்க்கையை பாதிக்க கூடும். அதனால் நாங்கள் இந்த ஆய்வை மேற்கொள்ள முற்பட்டோம்.

ஆய்வின் நோக்கம்

சர்க்கரை நோயாளிகளுக்கு வரக்கூடிய நுரையீரல் பாதிப்புகளையும் மற்றும் உடம்பில் சர்க்கரையின் அளவை மாற்றக்கூடிய வேறுபல காரணயுக்திகளோடு ஒப்பிட்டு பார்த்தல்.

ஆய்வில் பங்குபெறும் நபர்களின் எண்ணிக்கை

60 (அறுபது)

ஆய்வு மேற்கொள்ளும் இடம்

உடலியங்கியல் துறை, பி.எஸ்.ஜி மருத்துவ கல்லூரி வளாகம்

ஆய்வின் பலன்கள்

இந்த ஆய்வு கூட விசாரணைகளை செய்வதினால், சர்க்கரை நோயாளிகளுக்கு ஏற்படும் நுரையீரல் பாதிப்புகளை தவிர்க்க முடியும்

ஆய்வினால் ஏற்படும் அசௌகரியம்

எந்த பக்க விளைகளும் இல்லை

இந்த ஆய்வில் கிடைக்கும் தகவல்கள் 15 வருடங்கள் பாதுகாக்கப்படும். இவை வேறு எந்த ஆய்விற்கும் பயன்படுத்தப்பட மாட்டாது. எந்த நிலையிலும் உங்களை பற்றிய தகவல்கள் யாருக்கும் தெரிவிக்கப்பட மாட்டாது. அவை இரகசியமாக வைக்கப்படும்.

இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொள்ளுவதால் எந்த விதமான பலனும் உங்களுக்குக் கிடைக்காது. எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு. ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சையில் எந்த வித மாற்றமும் இருக்காது.

இந்த ஆராய்ச்சிக்காக உங்களிடம் சில கேள்விகள் கேட்கப்படும். சில இரத்த மாதிரிகள் அல்லது திசு மாதிரிகள் எடுக்கப்படும்.

மேலும் இந்த ஆய்வில் பங்கு கொள்வது உங்கள் சொந்த விருப்பம். இதில் எவ்வித கட்டாயமும் இல்லை. நீங்கள் விருப்பப்பட்டால், இந்த ஆய்வின் முடிவுகள் உங்களுக்குத் தெரியபடுத்தப்படும்.

ஆய்வாளரின் கையொப்பம்

தேதி

ஆய்வுக்குட்படுபவரின் ஒப்புதல்

நான் இந்த ஆராய்ச்சியின் நோக்கம் மற்றம் அதன் பயன்பாட்டினைப் பற்றி தெளிவாகவும், விளக்கமாகவும் தெரியப்படுத்தப்பட்டுள்ளேன். இந்த ஆராய்ச்சியில் பங்கு கொள்ளவும். இந்த ஆய்வில் மருத்துவ ரீதியான

குறிப்புகளை வரும் காலத்திலும் உபயோகப்படுத்திக் கொள்ளவும் முழு மனதுடன் சம்மதிக்கிறேன்.

ஆய்வுக்குட்படுபவரின் பெயர் -

முகவரி -

கையொப்பம் -

தேதி -

ஆய்வாளரின் தொலைபேசி எண். - 9715874362

மனித நெறிமுறைக்குழு அலுவலகத்தின் தொலைபேசி எண். – 0422 2570170, Extra – 5818

இந்த ஆய்வுக்கு உதவியதற்கு நன்றி

ANNEXURE – IV

DATA COLLECTION TOOL

NAME :

AGE :

GENDER :

OCCUPATION :

HEIGHT :

WEIGHT :

BMI :

FAMILY HISTORY :

TREATMENT HISTORY :

ARE YOU ON TREATMENT FOR ANY OTHER CHRONIC DISEASE

(LIKE HYPERTENSION, ISCHEMIC HEART DISEASE MYCADIAL INFARCTION)?

PERSONAL HISTORY (ALCOHOLIC / SMOKING / TOBACCO CHEWING):

SIGNATURE OF PARTICIPANT

STUDY GROUP								
S.NO.	**AGE**	**FEV1/FVC**	**FVC**	**FEV1**	**FEF25-75**	**PEFR**	**BMI**	**HbA1c**
2	45	86.3	76	79	44	111	27.4	6.8
2	47	83.2	66	64	61	75	17.2	6.9
2	39	88	103	93	85	94	30.8	9
2	46	75.9	59	53	28	48	26.3	8
2	42	82.8	79	76	61	110	23.5	6.8
2	49	90.4	73	76	80	96	23.6	8.2
2	49	88.1	79	82	126	111	28.6	10
2	53	88.1	79	82	64	92	25.1	7
2	41	81.5	79	76	43	67	19.5	10.1
2	52	90.8	79	82	80	99	23.6	8.6
2	46	89	79	73	68	78	31.1	6.1
2	48	68	86	66	48	45	25	7
2	45	69	109	84	42	93	26.6	6.9
2	38	91.7	79	87	75	98	32.8	9.8
2	33	86	98	87	97	80	25.9	10
2	58	88	46	51	49	74	38.4	10
2	37	81.9	67	67	51	82	34.1	6.5
2	45	85.8	89	91	67	91	24.8	10.5
2	45	84.6	80	80	65	93	25.3	7.6
2	34	84	132	112	115	95	27	6.8
2	33	86	104	91	96	100	25.5	6.4
2	40	86	66	62	99	81	27.9	7.2
2	43	77	96	76	29	49	28.3	7.1
2	45	85.2	81	85	75	97	24.8	7.1
2	46	84	108	97	88	89	29.7	5.8
2	45	78	89	72	49	82	22.3	7
2	45	90.1	69	73	71	113	28.8	8.1
2	40	74.8	50	47	27	51	23.4	7.9
2	54	85	69	72	59	82	27.2	6.9
2	44	81	86	75	65	91	27.9	6.61

CONTROL GROUP								
S.NO.	AGE	FEV1/FVC	FVC	FEV1	FEF25-75	PEFR	BMI	
1	35	78.6	110	105	72	105	25.3	
1	40	90.6	81	86	89	103	31.6	
1	48	75	121	94	49	84	25.9	
1	40	85.9	85	82	73	95	27.3	
1	38	87	85	86	78	87	18.7	
1	40	81	90	85	59	76	27.5	
1	39	81	124	103	69	97	22.2	
1	44	85	107	95	81	100	29.5	
1	45	87	112	102	93	113	26	
1	41	73	118	89	68	94	30.1	
1	49	86.2	80	82	71	80	34	
1	54	77	113	90	65	62	34.1	
1	50	87	117	104	99	106	22.7	
1	48	79	118	98	85	86	24.2	
1	38	90.5	111	118	125	112	24.5	
1	35	82.9	84	85	57	89	21.4	
1	36	81	129	117	102	117	31	
1	48	90.3	92	97	91	103	22.5	
1	48	81	103	85	53	83	23.5	
1	40	81.9	82	81	60	83	28	
1	42	91	99	91	120	138	26	
1	40	80.08	85	80	56	101	26.9	
1	38	83.3	87	87	68	97	33.9	
1	44	81.3	81	80	53	92	30	
1	35	85.39	84	84	71	101	26	
1	44	84.4	88	98	94	107	24.5	
1	46	77.52	82	73	50	74	23.5	
1	40	76	118	90	64	76	23	
1	48	87	99	87	86	115	31	
1	46	81	112	92	44	97	26.2	